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MALARIA

WITH SPECIAL REFERENCE TO THE AFRICAN FORMS

by

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FOREWORD

There is something very satisfying in the practice of tropical medicine Apart from the fascinating life cycles of so many of the parasites which infect human beings, a large number of tropical diseases make nicely rounded-off studies There are hiatuses of course but the etiology is usually known, clinical features have been closely studied, the diagnosis is capable of definite proof by easy means there are a number of excellent remedies and a great deal is known of prophylaxis These aspects are all thoroughly exemplified in malaria, the most important of all tropical diseases

There is, however, also a difficult side to the case It used to be said of syphilis that if you knew it you knew the whole of medicine Malaria comes near to deserving the same description Its clinical manifestations are protean It may simulate a vast number of other clinical conditions To confound matters even more it is frequently found together with other diseases in the same person at the same time (an important aspect of tropical medical practice) Moreover, when another disease manifests itself clinically, a malarial infection, otherwise latent, tends to become active

It is not only in tropical parts that the medical man needs to be ever alert for the occurrence of malaria If the patient has been where he could have become infected malaria must always be seriously considered no matter in what guise the disease presents itself Outside of malarious areas there is a tendency to think of malaria only when there are typical paroxysms that is often but to give a name to what is practically self-evident

It is against this general background that Dr Blackie with his extensive experience, has dealt with the subject clearly, concisely and accurately This monograph on malaria is a well balanced and practical presentation of the subject

F FORMAN, M D, F R C P,
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CHAPTER ONE

HISTORICAL REVIEW

In the geographical zone that lies between the Tropic of Cancer and the Tropic of Capricorn, malaria is almost universally present as an endemic disease of varying intensity. It is seldom found over 6,000 feet, and in certain desert areas where the mosquito vector cannot breed, so that even in the Tropics non-malarious areas exist.

Pl falciparum constitutes the prevailing species throughout the tropical belt, but is also found wherever the seasons are characterised by a sub-tropical summer and a mild winter Consequently *Pl. falciparum* is found extending into Northern Africa and across the Mediterranean to Southern Europe

Pl vivax covers an even more extensive geographical zone in that it is distributed sporadically throughout the Tropics and sub-tropics and is found in the Temperate Zone as far north as 60° N in the vicinity of Lake Ladoga in Russia and Southern Sweden, while in the Southern Hemisphere it extends as far south as South Queensland (20° S), Northern Argentina and Natal (30° S)

Pl malariae has a very much more restricted distribution, and although it may constitute the prevailing species in localised areas of tropical Africa, Ceylon and the Malay States, it occurs sporadically throughout Central and West Africa It is found in Central Europe, e g , Macedonia, and in the countries of the Near East, such as Syria, Palestine and Iraq In the Far East it has been found in the Andaman Islands, India, Central and South China, while in the New World it occurs as a rare infection in the West Indies, Brazil, Panama, Central America, Mexico and in the Southern United States

Like *Pl malariae*, *Pl ovale* appears to be confined to a limited area, being found especially in East and Southern Africa, but infections have also been reported from the Philippines, New Guinea, Russia, Persia, Palestine, India, China, Mauritius and South America

The distribution of malaria and the various plasmodial species is mainly a question of atmospheric temperature and humidity, but additional factors such as soil chemistry, altitude, racial immunity and local economics all contribute to the incidence of the disease both as a seasonal and as an endemic malady in any given locality

Wherever malaria prevails in a highly endemic form, the tendency is for the indigenous inhabitants to build up a considerable measure of immunity to the disease, so that the acute paroxysms of infancy and early childhood gradually give way to a smouldering infection virtually devoid of clinical expression That is to say, a state of premunity prevails and is maintained only so long as the infection *persists in the tissues of the host* For this reason acute malaria is seldom encountered amongst the adult population of an endemic area where re infection is taking place continuously Only in the presence of hyperinfection or of some debilitating illness are acute symptoms likely to appear, and even then are readily eliminated therapeutically Furthermore, the comparative freedom of the adult section of, for example the African native from the acute manifestations of malaria is all the more remarkable when it is borne in mind that he is being simultaneously assailed by the debilitating influences inherent in polyparasitism and avitaminosis

The intrusion of the non immune European into the malarious zones of the Tropics has, however, brought the clinical features and after effects of acute malaria into sharp relief Not only are the immediate consequences of infection more damaging and more dramatic, but recurrent infection leads to progressive deterioration in the patient's general health, and in the case of young children may gravely retard development of mind and body

It follows, therefore, that in the case of Europeans, neglected malaria not only exacts a high toll of life, but may engender a state of physical and psychological deterioration and thereby exerts an adverse influence on the economic efficiency and moral standards of those upon whom the ultimate success of all colonisation schemes must depend

From the clinician's viewpoint, however, malaria has two great redeeming features Firstly, accurate diagnosis is possible in the great majority of malarial cases This is particularly so in acute

malaria, but even the chronic forms present many characteristic features Secondly, we have a series of powerful plasmocidal drugs which enable the clinician to bring the acute forms of an attack under rapid control, provided a diagnosis has been arrived at expeditiously Finally, with the introduction of new and potent insecticides, the hygienist is now in a position to intensify his attack on the insect vector and so restrict the spread of the disease

The outlook for the future is thus full of promise, but it may be well to pause at this point and pass in review the labours and inspirations of those men who have made possible the recent advances in the fight against malaria

Before the doctrine of the mosquito-transmission of malarial infection was postulated, malaria was associated in the minds of men with swamps and marshes, even though the discrepancies that existed between "marsh fever" and marshy areas was fully appreciated It was long believed that the miasmata rising from tropical swamps constituted the immediate source of the fever, although as time went on there was considerable speculation concerning the precise nature of the fever producing components of these telluric emanations

About the middle of the 19th century Hensinger, Mitchell and others endeavoured to clarify the position by postulating a parasitic cause for malaria This suggestion led Massy of Ceylon to claim that a microscopic fungus could be recovered from the atmosphere wherever malaria was prevalent, and later Holden made a special study of a malarial outbreak on shipboard, and not unnaturally isolated Thallophyta from infected store rooms. He believed that Thallophyta were only capable of causing the disease in combination with H_2S from the stagnant water of the holds In due course Algae were postulated first by Van den Corpat and later by Balestra as the primary cause of malarial fever Thus Scott quotes Balestra as saying that he 'took fever twice after drawing deep breaths over a vessel containing water from the Pontine marshes of the Roman Campagna, in which algae were present"

Then in 1879 Klebs and Tommasi Crudeli described rods and oval motile spores which "when isolated and cultivated produced the most marked malarial sickness in the animals which received them " From their description of the morbid anatomy of their experimental

animals, it is probable that these investigators were dealing with *B anthracis* They named their organism *Schizometes bacillaris*, and claimed to be able to isolate it from the soil of the Roman Campagna They then built up an ingenious theory to the effect that for physical reasons these microbes lay like a ground fog over and around the marshes, and would therefore be inhaled by anyone walking in the vicinity

Thus until 1880, malaria was regarded as a disease that followed exposure to the miasmata that rose from marshes, lakes or rivers What the "malarious substance" might be was uncertain, but was probably some lowly form of life, either algal, fungal or bacteria in character

Then came one of the most momentous discoveries in the history of malaria—the discovery of the causal parasite by Alphonse Laveran on the 6th November, 1880 This was followed in 1881 by a detailed description of "certain parasitic elements," which he had succeeded in demonstrating in the peripheral blood of his malaria patients He regarded the parasite as a species of Oscillaria, and named it *Oscillaria malariae* After some controversy Laveran's findings were finally confirmed and extended by Richard in North Africa, Marchiafava in Italy, and in due course by workers in other parts of the world

As morphological and clinical details accumulated, it became apparent that more than one species of parasite was concerned in human malaria, and eventually four distinct species came to be accepted But in spite of the wealth of parasitological detail that was being amassed, the whole question of transmission remained unsolved, and as yet nothing had occurred to upset the inhalation theory But it may be said that the first step towards solving the riddle was taken when the phenomenon of ex flagellation of the microgametocytes was observed While the Italian observers Bignami and Grassi regarded ex flagellation as evidence of dissolution, Manson was convinced that it constituted an integral part of the plasmodial life cycle Manson's views were eventually confirmed in 1897 by W G MacCallum of Johns Hopkins University, who was able to demonstrate impregnation of the female malarial gametocytes by the flagella extruded by the male forms Meanwhile, attention was being attracted to the possibility of malaria being an insect-

transmitted disease It does not appear possible to say where or with whom the idea arose In the first place it was already known that certain plant and animal diseases were transmitted by biting insects, and for several centuries before the discovery of the plasmodia, the indigenous inhabitants of malarious regions had vaguely associated marsh fevers with mosquitoes

Then, in 1879, the insect transmission of human disease became an established fact when Manson demonstrated the transmission of *Wuchereria bancrofti* by the *Culex* mosquito While the wider implications of this important discovery were not immediately appreciated, it undoubtedly constituted the foundation of Ross's work on the mosquito transmission of malaria nearly 20 years later

It is not proposed to give in detail the inspiring story of Ross's work in India during the years 1895 to 1898 which culminated in the discovery of the mosquito transmission of the avian plasmodium The story is fully expounded by Sir Harold Scott in his scholarly *History of Tropical Medicine* However, it is of interest to glance briefly at the steady growth of the conviction that malaria was a mosquito-borne disease long before the experimental proof became available

In 1883 King in America put forward the view, based on 19 points, that mosquitoes constituted the vectors of malaria, but just how transmission occurred was a matter of surmise and controversy Both Manson and Laveran held the view that malaria could be acquired by drinking water in which mosquitoes had died after feeding on a malarious patient or by inhaling dust from dried-up mosquito-haunted pools So obsessed was Manson with the association of malaria and stagnant water that he administered to human volunteers a concoction of malarial blood and sterilized marsh water after a suitable period of incubation—a procedure stigmatized by Darwin as a fool experiment! Manson had already shown that the nsect transmission of a human parasite (*W bancrofti*) occurred as true biological (as opposed to a "mechanical") phenomenon in hich a vital phase of parasitic development took place in the sues of the insect host and in connection with the malaria parasite was convinced that the phenomenon of ex flagellation constituted lence of a life cycle outside the human body

by a process of inductive reasoning Manson formulated the

mosquito-malaria hypothesis He himself was prevented by circumstances from working out his idea, so that it fell to Sir Ronald Ross, to whom Manson communicated his views, to carry through the long series of experiments which in 1898 established the truth of Manson's theories

Ross began his "historic quest" in India in 1895, and soon showed that *the phenomenon of ex-flagellation took place in the stomach* of a dapple-winged (anopheline) mosquito, and later on found that the flagella soon disappeared, or at least could no longer be recognised in the mosquito's stomach Then at Secunderabad in 1897 he saw pigmented cysts (oöcysts) in the stomach wall of laboratory-bred mosquitoes, of the spotted-wing variety which had fed on malarious patients, so that now he was reasonably certain he had found the species concerned in malaria transmission He saw, too, the rupture of the oöcyst, whereby the sporozoites were released into the body cavity of the mosquito with some eventually reaching the tissues of the salivary glands

At this juncture Ross's investigations were temporarily suspended by reason of his transfer to a non-malarious district in Rajputana, but on his return to Calcutta he was urged by Manson to follow McCallum's lead and utilise avian malaria in his final experiments *This he did, and in 1898 succeeded in tracing* the developmental cycle of the avian plasmodium through all its phases, and finally succeeded in establishing the truth of Manson's hypothesis by carrying out a series of transmission experiments by the bite of infected anopheline mosquitoes

All that now remained to be done was to verify these findings in relation to human malaria, but an ill-fated transfer to Assam on a new problem denied to Ross the final discovery Instead the problem was taken up and carried to finality by the Italian workers Grassi and Bignami, who confirmed Ross's work and established the mosquito transmission of human malaria

In the years that have followed these brilliant discoveries, a wealth of biological detail has been accumulated round the vectors of malaria in all parts of the world, so that present day control measures are based on accurate knowledge of the bionomics of the mosquito host

Again, a keener appreciation of the natural history of malaria

in man has led to greater precision in its therapeutics, while quinine, which has long held pride of place as the drug of choice in malaria, is now being rivalled and to some extent replaced by a series of synthetic plasmocidal drugs The first of these was prepared at Elberfeld in 1924 and tested against avian malaria in 1926 It was originally termed biprochin, but later became known as plasmoquine Plasmoquine is a synthetic quinoline derivate which destroys the schizonts and gametocytes of *Plasmodium vivax*, *Pl ovale*, *Pl malariae* and the gametocytes but not the schizonts of *Pl falciparum* except when combined with quinine in the form of plasmoquine compound

Further investigations led in 1930 to the production of Erion or Plasmoquine E, a synthetic acridine derivative which was later termed Atebrin Since the drug is now manufactured in several parts of the world, it is variously known as mepacrine, quinacrine, haffkinine and crinodora Its plasmocidal action is analagous, to quinine in that it destroys all forms of *Pl vivax*, *Pl ovale* and *Pl malariae* In the case of *Pl falciparum* infections it destroys the schizonts but not the gametocytes

Finally, the latest synthetic plasmocidal drug to appear was prepared in England by the Imperial Chemical Industries under the name of Paludrine, and the preliminary trials show a high order of therapeutic efficiency

This brief historical review brings us back to the malaria problem of the present day

The disease continues to be widespread throughout the length and breadth of the Tropics and beyond, and in consequence is responsible for a heavy toll of life, both amongst the indigenous inhabitants and amongst European settlers In addition it is responsible for much in the way of chronic ill health and invalidism

But recent advances in chemo-therapy have provided the clinician with new and powerful drugs for the more efficient treatment of the disease in all its phases, and at the same time refinements in laboratory technique have enhanced the accuracy of laboratory diagnosis

Again, in the sphere of preventive medicine, the hygienist is now in possession of highly potent insecticides by means of which he can strike at the very heart of the malaria problem—the mosquito vector

None the less, the scientific control and elimination of malaria

will long remain a task of the first magnitude but the balance is now more definitely weighted in favour of those who are grappling with this elusive biological challenge to human life and enterprise

CHAPTER TWO

PARASITOLOGY

Human malaria is conditioned by an infection with protozoa which belong to the class Sporozoa, suborder Haemosporidia, genus Plasmodia The various members of this genus exhibit a biphasic life cycle whereby one developmental phase occurs within the tissues of an invertebrate host—the female anopheline mosquito, and the other takes place within the endothelial and the red blood cells of the human host

The mosquito phase represents the sexual cycle or sporogony which is initiated by fusion of the sexual forms of the plasmodium within the mosquito's stomach and is followed by gradual evolution of an oöcyst in which develop vast numbers of sporozoites These are subsequently transmitted to the human host by the bite of the mosquito From the biological view point, the mosquito constitutes the definitive host of the plasmodium with man the intermediate host The human or corporeal phase of the cycle follows upon the inoculation of the human host with sporozoites from an infected mosquito On entering the red blood cells an asexual developmental process known as schizogony occurs This process, which is confined to the red blood cells, results in the formation of a number of daughter spores or merozoites, the sudden release of which into the blood stream precipitates the febrile paroxysms which constitute the classical presenting clinical feature of acute malaria These pyrogenic forms, however, are incapable of infecting the mosquito host, and are therefore valueless from the point of view of propagating the plasmodial species

Hence, an additional developmental phenomenon can be observed during the corporeal phase, and consists in the evolution of sexual forms or gametocytes which, though without influence on the febrile paroxysms, render the blood infective to the carrier mosquito The term gametogony is applied to this process, and by this means a

biological link is forged between the human and mosquito cycles
Thus the full life cycle of the malarial parasite is made up as follows

1 Sporogony which takes place in the female anopheline mosquito and from the view point of human malaria represents the extra-corporeal phase of the cycle

2 Schizogony and gametogony, both of which occur within the red cells of the human host, the former precipitating acute febrile paroxysms and the latter rendering man infective to the mosquito

THE HUMAN PLASMODIAL SPECIES

There are at least four plasmodial species encountered in human malaria These are

1 *Plasmodium vivax* (Grassi and Feletti, 1890)
2 *Plasmodium ovale* (Stephens, 1922)
3 *Plasmodium malariae* (Laveran, 1881)
4 *Plasmodium falciparum* (Welch, 1897)

These four species of malaria parasite can be differentiated morphologically throughout their developmental cycle in the human host, and in view of the clinical implications inherent in the species differentiation a systematic description of the plasmodia will be given later Meanwhile a more detailed picture of the biology of the life cycle common to all four species will be described

THE PLASMODIAL LIFE CYCLE

As already stated, the life cycle of the malaria parasite is biphasic in character, consisting of (*a*) the Human Phase (sometimes referred to as the corporeal, endogenous or asexual phase or the phase of schizogony), and (*b*) the Mosquito Phase (or the extra-corporeal, exogenous or sexual phase or the phase of sporogony)

THE HUMAN PHASE SCHIZOGONY

The human host is infected through the bite of a female anopheline mosquito when sporozoites are injected into the subcutaneous tissues

The immediate fate of the sporozoites is still *sub judice*, but there is increasing support for the view that they gain access to the *cells* of the reticulo-endothelial system, in which they undergo a preliminary stage of development before entering the red blood cells This

phase, which is variously referred to as the 'X'-cycle, the first tissue stage or the exo-erythrocytic cycle, has been amply demonstrated in the case of certain avian plasmodia, e g , *Pl relictum*, *Pl gallinaceum*, *Pl lophurae*, while similar claims have been made in connection with the human plasmodia

In the case of avian plasmodia the exo-erythrocytic forms appear as non pigmented bodies within the cytoplasm of macrophage cells in the liver, spleen, bone marrow, and eventually in the endothelium of blood vessels in various parts of the body. They appear to undergo a form of division with the formation of daughter spores or merozoites which on escaping from the parasitised cell not only enter cells of a similar class, but also invade the red blood corpuscles

This remarkable phenomenon not only provides a clue to the vagaries of chemoprophylaxis, but may also constitute the basis of clinical relapses in the therapeutics of malaria

Eventually, however, the parasite appears in the red cells as a thin, crescentic ring of cytoplasm surrounding a central vacuole with a small chromatin dot or dots lying on the crescent at its most tenuous part This growing form is known as a trophozoite

The number of trophozoites in a given red cell may vary from one to several, depending to some extent on the intensity of the infection, but more especially on the species of the infecting plasmodia As will be seen later, multiple parasitism of the red cells is a common event in heavy infections with *Pl falciparum* As the trophozoite matures it assumes an irregular, amoeboid outline with fine filamentous strands of protoplasm extending out into the substance of the red cell It is possible, of course, that the plasmodium lives on the surface of the red cell rather than within its substance, but it is not necessary to delay over this controversial point which does not affect the developmental pattern

Since the growth of the parasite takes place at the expense of the red cell, modifications occur in its staining reactions, to an extent which may be utilised in species diagnosis In addition to the chromatic changes which in the presence of an appropriate staining technique can be shown to consist in either stippling or decolourisation the red cell may be demonstrably enlarged or may appear more compact and solid than usual In one variety of stippling, the red cell is covered with fine, pink spots known as Schuffner s dots This type

of stippling is seen in infections with *Pl vivax* and *Pl ovale*

Another variety consists in the formation of coarse red dots with a coccoid, cuneiform or irregular outline They are never more than a few to a red cell, and are known as Stephen's and Christopher's or Maurer's dots

It does not appear that young red cells (reticulocytes) are infected with greater frequency than the more mature forms, even though some workers claim to have shown that in *Pl vivax* infections particularly the plasmodia exhibited a predilection for the reticulocytes

As the parasite develops, yellowish brown granules known as malarial pigment appear within the cytoplasm, representing a special degradation product of haemoglobin, and therefore an excretory product of the plasmodial metabolism The quality and quantity of the malarial pigment varies as between one plasmodial species and another

As the parasite gradually fills the red cell, amitotic division of the chromatin dot occurs and continues until from eight to 32 subdivisions have formed As division of the cytoplasm occurs simultaneously, each daughter nucleus comes to be contained in a small fragment of cytoplasm, thereby giving origin to a group of new spores or merozoites which lie enclosed within the red cell envelope

The merozoites tend to be disposed round the central mass of pigment and residual cytoplasm after the manner of a rosette

In due course the red cell membrane gives way, and the merozoites are scattered into the plasma, but they rapidly become attached to a new series of red cells and eventually penetrate the cell membrane to initiate a further developmental cycle

The pigment released by the rupture of the red cells is taken up by the cells of the reticulo-endothelial system in the spleen, liver and elsewhere

THE HUMAN PHASE GAMETOGONY

From the biological view point schizogony is a sterile phenomenon which would lead automatically to the extinction of the plasmodial species, but in order to maintain continuity with the definitive host a morphological variant appears from amongst the merozoites, sometimes quite early on in the malarial attack, or it may be after a delay of several days These variants are destined to become the

sexual forms of the plasmodium, and are designated gametocytes Initially they appear as globular structures which develop within and gradually fill or even distend the red blood cell During development they exhibit little or no amoeboid activity, and when suitably stained have a more compact appearance than the developing schizonts, while it is usually possible to distinguish between the male and the female forms Thus the cytoplasm of the male gametocyte (or microgametocyte) stains a faint blue, the nucleus is composed of fine chromatin granules centrally situated but loosely dispersed over a fairly wide area, while the pigment consists of a fine granular deposit.

In the case of the female gametocyte (or macrogametocyte) the cytoplasm stains a deep blue, the nucleus is deeply stained and compact with the pigment a coarse yellow-brown colour

The detailed morphology of the gametocytes varies with the plasmodial species but is globular in all the recognised species with the single exception of *Pl falciparum* in which crescentic forms appear

The process of gametogony ends with the fully grown parasite occupying the red cell where it remains in a dormant phase until taken up and reactivated by the appropriate anopheline mosquito

THE MOSQUITO PHASE SPOROGONY

The sexual phase of the life cycle (or sporogony) is initiated within the stomach of the mosquito where the gametocytes escape from the red cell envelope to form a spherical body, whatever its original shape By means of reduction division a process of maturation follows, during which portions of nuclear substance are probably extruded as polar bodies

The nucleus of the male gametocyte breaks up to form from four to eight divisions, each of which acquires a thin filament of cytoplasm, and by a process of vigorous flagellation succeeds in breaking away from the parent cell This new body is now termed a microgamete

The female gametocyte undergoes a similar process of maturation, but apart from extruding two chromatin fragments or polar bodies the nucleus remains intact and the cell globular The cell thus modified is now the macrogamete, and as such is capable of being fertilised Fertilisation is effected by the actively motile microgamete

which penetrates the cytoplasm of the macrogamete, whereupon fusion of the nuclear elements of the cells ensues The fertilised macrogamete is now referred to as the zygote, which rapidly changes to become an actively motile body termed the travelling vermicule or oökinete It penetrates the gastric epithelium and finally comes to rest immediately beneath the delicate outer membrane of the mosquito's stomach, where it rounds up to form a minute transparent structure or oöcyst which at this stage measures 6μ to 12μ in diameter, and consists of a single vesicular nucleus enclosed in cytoplasm As the oöcyst matures it increases in size, the cytoplasm becomes vacuolated and the nucleus subdivided with the production of a series of chromatin granules which are distributed on the protoplasmic strands In due course each granule becomes the centre of an acicular cytoplasmic structure or sporozoite arranged in radial fashion within the oöcyst When fully matured each oöcyst *measures from 40μ to 60μ in diameter and contains thousands of* sporozoites An infected mosquito will carry an average load of some 20 oöcysts, but counts as high as 500 have been recorded

On attaining full maturity the oöcyst ruptures and the sporozoites escape into the body cavity of the mosquito, and by virtue of their motility they migrate anteriorly to the salivary glands where they eventually appear in heavy concentration, although most other parts of the insect's body become infiltrated to a greater or less extent

The sporozoites measure 14μ to 15μ in length and carry either one or more nuclei The mosquito is now infective to man, and in the act of biting, the sporozoites are carried down in the salivary secretion and thus gain access to the human host

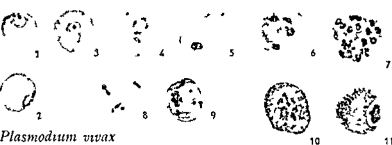
NOMENCLATURE AND DESCRIPTION OF THE MALARIA PARASITES

PLASMODIUM VIVAX

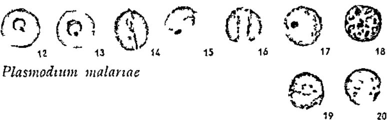
(Grassi and Feletti, 1890)

Synonyms Haemamoeba malariae var tertianae (Celli and Sanfelici, 1891) , *Haemamoeba malariae var magna* (Laveran (in part), 1900),

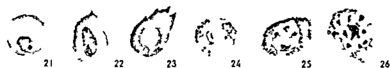
Except where otherwise stated the morphology of the malaria parasite will be described as it appears in smear preparations stained either by Leishman's or Giemsa's technique



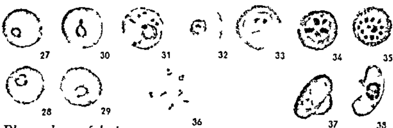
Plasmodium vivax



Plasmodium malariae



Plasmodium ovale



Plasmodium falciparum



Plasmodium tenue

(To face page 14)

KEY TO MALARIA PARASITES

1 11 *Pla mod im vivax*
1 Smallest ring (about one third d ameter of cell)
2 Accole form S milar forms occur in all the spe ies but are not sho vn
3 R
4
5
6
7 1
8
9
10
11

12 20 *P malariae*
12 Smallest ring (about one third diameter of cell)
13 Ring form showing a pigment grain
14 *Ribbon form*
15
16
17
18
19
20

21 26 *P ovale*
21 Smallest ring (about one third diameter of cell)
22 Partially grown schizont showing lobose form as in quartan st ppl ng is not shown but should be present if sp imen were properly sta ned
23 Same showing appearance not uncommonly seen stippling should normally be present in well stained preparation
24 Partially grown schizont with stippling shown compare Fig 4 (*P vivax* in wh ch amoeboid processes are very evident at this stage)
25 Maturing schizont
26 Mature schizont

27 38 *P falciparum*
27 Smallest ring (about one sixth d ameter of cell)
28 Ring with double chromatin mass
29 Same with fine hair like cytoplasm
30 Commencing amoeboid changes compare size of ring in Fig 3 (*P vivax*)
31 Largest ring form showing Maurer s stippling
32 Most advanced stage usually seen in peripheral circulat on (Maurer s

33
34
35
36
37
38

39 44 *P tenue*
39 Smallest ring (about one sixth d ameter of cell)
30
41
42
43 irger and more commonly seen Maurer s stippl n as in Fig 42 would normally be present in well sta ned films
44 Form similar to Fig 33 but commonly present in peripheral blood

When the sporozoites reach the red blood cells they form a ring-like body which measures about 2·5μ in diameter or approximately one third the diameter of the red corpuscle. The blue-staining cytoplasm is fairly abundant and is arranged crescentically round a vacuole which Schaudinn regarded as a food vacuole. The nucleus appears as a bright red marginal dot of chromatin which may sometimes be situated nearer the centre of the ring.

As development proceeds, the ring appearance is maintained but the cytoplasm increases in amount and the chromatin dot enlarges. Gradually, however, the parasite assumes an irregular shape, and when examined in the fresh state during this phase of development it exhibits a lively amoeboid activity as revealed by the vigorous extension and retraction of the peripheral pseudopodia. In stained preparations the amoeboid activity is reflected in the irregular outline of the projecting pseudopodia. As the parasite merges from the ring to the amoeboid stage, fine pigment granules appear within its cytoplasm, and in fresh preparations these show active Brownian movement. When stained they appear either as brown or black granules. With the approach of nuclear segmentation, amoeboid movements become more sluggish, the vacuole vanishes and the plasmodium now appears as a compact rounded body which fills the greater part of the enlarging red cell Nuclear division sets in from 36 to 48 hours after invasion of the red cells, and leads to the formation of approximately 16 new chromatin particles, although the actual number varies from 12—24

Division of the cytoplasm then follows, so that each chromatin fragment acquires part of the original cytoplasm In this way a number of young forms or merozoites are evolved and are temporarily clustered within the red cell after the manner of a rosette or mulberry

Thus the fully matured schizont is composed of some 16 mero- [illegible]

or other side They rapidly penetrate or attach themselves to fresh red cells where the asexual forms reappear as rings to initiate a new schizogony cycle The cycle lasts approximately 48 hours and takes

place within the red cells of the peripheral circulation

The Parasitised Red Blood Cells in Pl vivax *Infections* Infection of the red blood corpuscles by *Pl vivax* initiates a series of characteristic changes in the parasitised cell, whether the infection be caused by the sexual or asexual forms of the parasite

Within a few hours of infection the red corpuscle begins to increase in size and simultaneously becomes paler in colour With the steady growth of the parasite a number of fine red dots of uniform size appear, and in due course stipple the entire red cell in a regular pattern These dots are termed Schuffner's dots—after their discoverer—and are never found apart from infections with *Pl vivax* and *Pl ovale* They enlarge slightly and become more defined as the plasmodium develops, and are regarded by Schaudinn and others as representing a fine precipitate in the substance of the red cell brought about by the colloidal disintegration which accompanies plasmodial absorption of the more readily digested components of the red cell structure It is important to bear in mind that the stippling affects the red cell, not the parasite, and furthermore that it can only be demonstrated when the blood films are stained in a medium of suitable alkalinity

Gametocytes The factors governing the onset of gametogony are not definitely known, but gametocytes are not usually demonstrable in the peripheral blood until after the completion of several schizogony cycles, although it must be admitted that young sexual forms have been observed in the course of the first febrile paroxysm

Young tertian gametocytes appear as small globular bodies staining blue with a chromatin particle situated either centrally or to one side Stained preparations may show a zone of perinuclear pallor, but vacuolation does not occur As growth continues the differential characters of the male and female gametocytes become more defined, so that when fully matured differentiation in stained preparations becomes relatively easy

The lively amoeboid activity of the schizont is never observed in the developing gametocyte which therefore remains round or ovoid throughout the intracorpuscular phase Full maturity is attained in six days

The female gametocyte fills the enlarged red cell and measures from 9μ to 10μ in diameter The cytoplasm stains a dark blue and

is densely infiltrated with a coarse yellow brown or brownish-black pigment The chromatin is concentrated to form a compact nucleus situated peripherally, and as already observed in the young forms, frequently shows a pale or colourless perinuclear zone—the "zone of caryolymph"

The male gametocyte remains smaller than the female, so that it never quite fills the enlarged red cell. For this reason Schüffner's dots may be demonstrable It has an ovoid shape and measures from 7μ to 8μ in its longest diameter The cytoplasm stains a faint blue or slate grey and contains abundant pigment in the form of fine rodlets or granules The nucleus consists in a loose reticular aggregation of chromatin granules distributed over a fairly wide area in the centre zone of the parasite

It should be noted that the rich pigment content of the gametocytes renders their recognition possible in unstained preparations when the active Brownian movement of the granules can be seen to best advantage by means of dark ground illumination

PLASMODIUM OVALE
(Stephens, 1922)

Pl ovale bears a general resemblance to *Pl malariae* except that the infected red cell is often elongated or oval in outline with a ragged margin, while the trophozoites are either round or oval

In stained preparations the ring forms of *Pl ovale* stain a deep blue with a prominent chromatin dot while even in this early phase numerous Schuffner's dots can be demonstrated in the infected red cell

From the ring stage the parasite matures without exhibiting any of the lively amoeboid activity of the *Pl viva* The schizont develops as a compact rounded or oval body which stains a deep blue and exhibits a tendency to assume band forms When nuclear division occurs the chromatin which stains a deep red or violet is distributed irregularly throughout the cytoplasm together with fine grains of light brown pigment When segmentation is complete the schizont contains from six to ten merozoites—usualy eight The schizogony cycle occupies 48 hours and takes place within the peripheral circulation

A characteristic feature of the parasitised red cell in *Pl ovale*

infections is the early appearance of prominent Schuffner's dots These dots appear much earlier than in *Pl vivax* infections where they are seldom observed at the "ring" stage

At the same time the red cell enlarges slightly, becomes progressively decolourised and assumes an oval shape with a ragged margin at one pole

The gametocytes of *Pl ovale* are compact rounded bodies bearing a close resemblance to *Pl malariae*, but occupying an oval shaped red cell in which Schuffner's dots are readily demonstrable. Differentiation from *Pl vivax*, however, is not always easy

PLASMODIUM MALARIAE
(Laveran, 1881)

Synonyms Haemamoeba laverani var quartana (Labbe, 1894) *Pl golgi* (Sambon, 1902)

The young ring forms occupy about one third of the diameter of a normal red cell, and measure from 2μ to $2\ 5\mu$ in diameter Intra corpuscular growth is relatively slow and at the same time there is

At all stages of development the parasite shows a tendency to assume the form of a band which crosses the full extent of the red cell, but does not necessarily lie in the long axis of the smear In these band forms the chromatin usually lies near one margin

The schizont slowly enlarges and may for a short time contain a vacuole, but whatever shape the plasmodium assumes, the nucleus is invariably situated near the edge

Pigment gradually develops in the form of a fine golden yellow granular material which accumulates on the margin directly opposite the nucleus, more especially in the case of the band forms

The schizont has a characteristically compact appearance, and when mature fills or practically fills the red cell which is neither decolourised nor enlarged.

Before the onset of nuclear division, the pigment, which by now has accumulated in considerable quantity, is distributed more diffusely throughout the cytoplasm as well as in the marginal zone Nuclear division leads to the formation of eight to 12 merozoites

symmetrically arranged around a loose mass of centrally placed pigment granules

The asexual cycle occupies 72 hours with schizogony occurring in the peripheral circulation

The Parasitised Red Blood Cells in Pl malariae *Infections* The red corpuscles are neither enlarged nor decolourised but may even appear smaller than neighbouring non-parasitised cells Very rarely and only after intensive staining a form of stippling known as "Ziemann's stippling" can be demonstrated in the form of scattered dots which, though resembling Schuffner's dots, are usually finer and fainter Since the stippling is not seen in the course of routine staining, the red cells in *Pl malariae* infections may be said to contain no diagnostic stigmata

Gametocytes The sexual forms are rounded in appearance with a large chromatin mass situated centrally

The fully developed macrogametocyte fills the red cell and shows a compact darkly staining nucleus situated peripherally in a cytoplasm which stains dark blue and in which basophilic granules appear The cytoplasm also contains aggregates of a light coloured pigment

The microgametocytes are usually present in low concentration in the peripheral blood Apart from being slightly smaller they stain more lightly than the female gametocytes, due to the fact that the chromatin is less concentrated and is frequently distributed in the form of an equatorial band

The pigment, though plentiful, is of a finer texture than in the female parasite The gametocytes grow slowly, and in the absence of nuclear division, may be difficult to distinguish from developing schizonts

PLASMODIUM FALCIPARUM

(Welch, 1897)

Synonyms The main synonyms include

Oscillaria malariae (Laveran, 1881, pro parte)
Haemamoeba praecox (Grassi and Feletti, 1890)
Haemamoeba immaculatum (Grassi and Feletti, 1890)
Laverania malariae (Grassi and Felitti, 1890)
Haemamoeba malariae praecox (Grassi and Feletti, 1892)

Plasmodium malariae praecox (Labbe, 1899)
Plasmodium praecox (Blanchard, 1900)

The earliest asexual forms demonstrable in the peripheral blood take the form of minute rings measuring about 1 5μ in diameter or about one sixth the diameter of a red cell or even less They are the smallest and finest of all the ring forms, and are easily distorted *in smear preparations*

The nucleus consists of a single circular granule of chromatin situated on or within the rim of cytoplasm which encloses the vacuole Sometimes the granule appears to be situated within the vacuole

With the rapid onset of nuclear changes the chromatin takes the form of a straight or slightly curved structure, or it may appear in the form of twin granules placed either contiguously or at opposite poles This binuclear appearance is a frequent finding in all infections with *Pl falciparum* Another highly characteristic feature of *Pl falciparum* infections is the occurrence of multiple infections of the red cells together with the tendency for the parasite to be silhouetted against the cell margin (appliqué or accolé forms)

The delicate rings gradually increase in size and give rise to what *is sometimes referred to as the signet ring appearance These forms* measure up to 4μ in diameter and are richer in cytoplasm with a well defined chromatin granule (or granules) which may project beyond the cell margin or may be within its substance In addition to the signet ring appearance, more amoeboid forms may be encountered in which traces of pigment may be demonstrable But some 18 to 24 hours after their appearance the rings disappear from the peripheral blood and only under conditions of exceptional gravity are the more mature developing stages encountered in the peripheral circulation

On leaving the peripheral circulation the parasites become solid, non vacuolated bodies with the pigment aggregated into a single round mass, while the chromatin is loosely distributed in contra distinction to the single compact chromatin granule of the other plasmodial species during early schizogony

The parasite continues to grow until it occupies about two thirds of the un enlarged red cell, when nuclear division recurs with the formation of from eight to 32 merozoites

The whole process of schizogony, which begins in the peripheral

circulation and is completed within the capillaries of the internal organs, occupies about 48 hours

The Parasitised Red Blood Cells in Pl falciparum *Infections.* The red cells do not enlarge, but in Giemsa stained preparations they frequently acquire a purplish tinge, and when deeply stained show a coarse stippling This stippling takes the form of a few coarse, irregularly shaped red dots, rings or loops, or may appear as a chromatin-coloured ring enclosing the parasite or demarcating the red cell margin These intracorpuscular deposits are known as Maurer's or Stephen's and Christopher's dots, and in view of their extreme rarity in quartan infections they are regarded as characteristic of infections with *Pl falciparum*

The phenomenon of auto-agglutination is frequently observed in infected red cells, and there is also a tendency for these cells to adhere to the capillary endothelium of the internal organs This latter observation is believed to offer at least partial explanation of the occurrence of schizogony within the capillary system of the internal organs

As will be seen below, the gametocytes assume an elongated crescent shape, and in so doing stretch the red corpuscle in such a way that it may appear as a dark red capsule surrounding the parasite, or at other times as a delicate bow-shaped line curving across the concavity of the crescent In such circumstances extensive decolourisation of the red cell has taken place

Gametocytes The gametocytes of *Pl falciparum* assume a characteristic crescentic shape and are commonly referred to as crescents

Initially they appear in the peripheral circulation as small, compact non vacuolated bodies which gradually elongate and take on

mately 12μ by 2μ to 3μ Morphological variants are frequently encountered, such as straight forms with tapering extremities or short stumpy forms

The female gametocytes are characteristically crescentic in outline with a cytoplasm which stains a dark blue The chromatin is collected into a centrally placed mass and is closely invested by the coarse pigment granules

The male gametocytes have a stumpy or oval appearance and the cytoplasm stains more lightly The chromatin is distributed over a wider area while the dark brown pigment is scattered throughout the cytoplasm in the form of coarse granules or rodlets

It should be noted that during the collection of blood samples the gametocytes may assume a globular shape This morphological change has never been observed as an intravascular phenomenon

CHAPTER THREE

PATHOLOGY AND MORBID ANATOMY

CLINICAL PATHOLOGY

HAEMATOLOGICAL FINDINGS THE RED BLOOD CELLS

The intracorpuscular distribution of the plasmodium leads to destruction of the infected red cells at the termination of schizogony, and at the same time cells that have been damaged by the malaria toxins are removed from the circulation by the phagocytic activity of the reticulo-endothelial system In this way an anaemia of the haemolytic type is induced The degree of anaemia will be determined by a variety of factors such as the severity of the plasmodial infection, the actual species of parasite concerned in the attack, the pre-existing state of the blood, the resources of the erythropoietic marrow, and so on For these several reasons a wide range in haematological values is encountered both in acute and in chronic malaria The lowest counts are usually found in association with subtertian infections, but in spite of this it may be stated that severe anaemia is not a feature of acute malaria In previously healthy Europeans the red cell count may fall to between 4 5 and 4 million cells per cubic millimetre following an acute attack of malaria, but it is certainly not common to find a count of less than 3 million The observation has also been made that the red cell count may begin to fall before the onset of the clinical paroxysms There is an associated fall in the haemoglobin values, so that a colour index of 0 9 may be regarded as an average finding

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red cell may be seen In the more chronic types of plasmodial infection giant semilunarshadow cells (the "corps en demilune" of the Sergents) are frequently seen as pale crescent shaped shadows

They take origin in the decolourised red cells which become enlarged and vacuolated, and subsequently break up to form semilunar shadows when blood smears are being prepared Cabot's rings and Jolly bodies are also frequently seen and may give rise to diagnostic errors if the possibility of their existence is overlooked Punctate basophilia occurs to a variable extent and is characterised by the presence of fine uniform basophilic granules which are difficult of recognition in over stained preparations

When severe grades of anaemia are induced by massive or recurrent plasmodial infections, it is not uncommon to encounter nucleated red cells (normoblasts) in the peripheral blood

On rare occasions the resultant anaemia conforms to the megalocytic type, but compared with pernicious anaemia, megalocytes are relatively few in the peripheral blood, hence it is doubtful if a widespread megaloblastic reaction occurs in the marrow

The presence of polychromatic cells in the blood has already been mentioned, and in vitally stained preparations the polychromatic cell has been identified with the reticulocyte

The behaviour of the reticulocyte in malarial infections has been closely studied, and it is now generally accepted that a slight but persistent increase in the reticulocytes occurs in the presence of a chronic plasmodial infection More significant, however, is the steady rise in the reticulocyte counts which attends the employment of plasmocidal drugs This rise is directly proportional to the degree of anaemia existing immediately prior to treatment, and attains maximal values between the sixth and tenth days following the onset of treatment It follows, therefore, that in these special circumstances a study of the reticulocyte count may supply indirect evidence of a chronic malarial infection The actual counts obtained during the treatment course may range from 3% to 30%

THE WHITE BLOOD CELLS

The white cells in malaria vary with the phase of the attack and the chronicity of the infection so that variable and apparently divergent figures are frequently quoted both for the total and for the differential white cell counts

At the outset of a malarial paroxysm a rise occurs in the total count, but as the attack develops and passes through its various

phases the count falls to normal and subnormal values during the apyretic interval

During the febrile phase the neutrophile percentage may remain within the normality range or a definite increase may be found During the afebrile phase, however, the haemogram shows a characteristic reduction in neutrophiles with an associated increase in lymphocytes and monocytes When the monocytes are studied throughout a series of malarial paroxysms it can be shown that their percentage varies inversely as the temperature—that is to say the monocyte percentage rises as the temperature falls

The monocyte in malaria appears as a large non granular cell rich in cytoplasm which may contain a few vacuoles and which stains a pale greyish blue The nucleus is situated eccentrically, is oval or round in outline, and stains a pale violet colour The chromatin is arranged in strands which are characteristically thickened at the points of intersection

Occasionally a very large form of monocyte is encountered in which the nucleus is banded, lobulated or horse shoe shaped Such forms are frequently referred to as the transitional cells of Ehrlich

In healthy normal blood the monocytes constitute from 4 % to 8% of the total white count, whereas in chronic or latent malaria the percentage may increase to between 15% and 30% or over

Where a monocytosis of this order is encountered in association with an appropriate clinical picture, it undoubtedly affords valuable presumptive evidence of malaria in those cases in which for one reason or another the plasmodium cannot be demonstrated in the peripheral blood On the other hand, it is important to bear in mind that there may be a complete absence of monocytosis in those who have been repeatedly exposed to plasmodial infections over a long period of time, as in the case of Africans in an endemic area

Again, monocytosis may arise in conditions other than malaria such as kala azar, amoebiasis glandular fever, rickettsiosis, and so on, hence the importance of assessing the differential white cell count in conjunction with clinical data

However, a study of the white cell count in malaria supports the view that a recurring febrile illness characterised by splenomegaly, leucopenia and a relative monocytosis of 10% or over may be

regarded as presumptive evidence of a plasmodial infection and justifies a course of anti malarial therapy

THE PIGMENTED LEUCOCYTE

A highly characteristic but relatively infrequent finding in blood smears prepared from malarial patients is the pigmented leucocyte

The leucocyte is usually a monocyte containing small clumps of malarial pigment within its cytoplasm Less commonly the pigment containing cell is a neutrophile polymorph

The presence of these pigment-containing cells implies that the patient is suffering from or has recently suffered from an acute attack of malaria

THROMBOCYTES

The chief significance of the thrombocytes in relation to malarial diagnosis lies in the possibility of their being mistaken for plas *modia When stained by Giemsa's method they appear as small* reddish violet bodies which may be round or oval in outline, so that when overlying a red cell they may simulate the malaria parasite but closer study will usually reveal the absence of a chromatin particle and of vacuolation in the cytoplasm During an acute malarial paroxysm the thrombocytes are reduced in number, but usually increase during the afebrile phase in conjunction with a leucopenic state of the white cell count

BIOCHEMISTRY OF THE BLOOD IN MALARIA

HAEMOGLOBINAEMIA

The demonstration of haemoglobinaemia in plasmodial infections presents many technical difficulties and so far no significant increase in the haemoglobin content of the plasma has been demonstrated even in the presence of massive infections On the other hand Schumm s test for methaemalbumin is usually positive, thereby providing indirect evidence of intravascular haemolysis

The absence of haemoglobinaemia can probably be explained by the steady absorption or conversion of haemoglobin by the plas modium during schizogony, together with the swift phagocytosis of all infected or damaged red corpuscles by the cells of the reticulo

endothelial system In this way haemoglobin released during sporulation must necessarily elude detection by current analytical methods

BILIRUBIN CONTENT OF THE PLASMA

The occurrence of excessive blood destruction in acute malaria leads to a demonstrable measure of hyperbilirubinaemia in most but not in all cases of the disease

In terms of van den Bergh units (taking 1 0 as the upper limit of normality) haematogenous bilirubin may range from 3 0 to 6 0 units with an average finding of 1 45 to 1 75 units These unit figures bear no direct relationship to the degree of anaemia prevailing in any given case but are determined essentially by the rate of blood destruction

The direct or biphasic van den Bergh reaction is not obtained in malaria except in the presence of some complicating factor such as cholelithiasis Thus in conformity with the intravascular haemolysis conditioned by plasmodial infection the qualitative van den Bergh test is positive in the indirect phase only

ALKALI RESERVE

Conflicting data have been obtained in acute malarial attacks but when the CO_2—combining power of the plasma is determined by the van Slyke technique no significant decrease in the alkali reserve can be demonstrated in uncomplicated cases of acute malaria

BLOOD UREA

Any slight rise in the urea content of the plasma in acute malaria is of a temporary nature and merely reflects the state of enhanced katabolism that normally accompanies any acute febrile condition

Permanent nitrogen retention would be consistent with permanent renal damage which rarely occurs in plasmodial infections except in quartan infections

BLOOD CHOLESTEROL

If the normality values for tropical patients be accepted as ranging between 120 and 200 mg per 100 cc then it will usually be found that hypocholesterolaemia predominates in acute malaria The fall in the cholesterol values coincides with the appearance of the

plasmodium in the peripheral circulations and persists until specific therapy is well established

It is of interest to note that the rise in cholesterol values parallels the rise in the reticulocytes

BLOOD SUGAR

Most observers record a normal blood sugar range in acute malaria, although there have been occasions in which a rise has occurred

SERUM PROTEIN FRACTIONS

There is a general reduction in the total serum protein, largely on account of a fall in serum albumin Euglobulin is increased to twice the normal values and pseudoglobulin is reduced

Lloyd and Paul have demonstrated a rise in the serum globulin-albumin ratio from the normal index of 0 66 to just below unity

SEDIMENTATION RATE

This is usually increased in acute malaria (Landeiro)

THE URINE

The urine is usually concentrated and highly coloured during the febrile paroxysm There is a characteristic increase in urobilin and urobilinogen (which is gradually converted to urobilin on standing)

A trace of albumin is commonly found, but clears up in the presence of efficient anti malarial treatment

On the other hand, a heavy albuminuria may develop and may constitute evidence of an acute parenchymatous nephritis In such cases the aetiological factor is almost invariably an untreated quartan infection, and it will usually be found that resolution of the renal lesion follows upon the elimination of the plasmodial infection

Very occasionally a transient glycosuria is noted in acute malaria

IMMUNITY IN MALARIA

The complex subject of immunity in malaria has been materially advanced by the study of the disease in the treatment of neurosyphilis and by the detailed immunological studies of Taliaferro and of Sinton on avian and simian malaria

It is now evident that immunity in malaria may be either natural or acquired

NATURAL IMMUNITY

The existence of a natural immunity to malaria is frequently encountered in groups of neuro syphilitics undergoing malaria therapy In these circumstances the patient may prove refractory to infection or, if infected, the resultant febrile paroxysms are extremely mild

In the same way clinical practice affords instances of a natural resistance to malarial infections amongst non immune groups Apart from variations in the severity of the febrile paroxysms, the incubation period may be protracted up to as much as six months Again, the existence of a natural immunity may be revealed by the presence of an occasional plasmodium in the peripheral blood with an entirely negative clinical picture When this occurs in the absence of any history of clinical malaria, it is logical to explain the phenomenon in terms of natural immunity

This immunity, however, may be restricted to one plasmodial species or even to one plasmodial strain

ACQUIRED IMMUNITY

Acquired immunity is met within areas of endemic malaria where it develops in response to repeated plasmodial infection In these circumstances recurrent pyrexia together with splenomegaly persists for a period of two or three years, and in due course a high degree of immunity is built up and will continue at a high level so long as the individual remains in the hyper-endemic area A high infantile mortality rate is exacted as the price of this immunity in any given community The usual measure of its existence is the spleen rate which remains more or less constant in any community with a high rate of tolerance, but the labile nature of the immunity is shown by the fact that any interruption in the active transmission of infection may at some later date be followed by a major epidemic and a high mortality rate The building up of a defence mechanism against malaria is a two fold phenomenon based on a proliferation and heightened activity of the macrophages or reticulo-endothelial elements together with the elaboration of specific antibodies which are probably of the nature of opsonins

The cellular changes occur mainly in the spleen, liver and bone marrow where the circulation is comparatively sluggish, thereby facilitating phagocytosis Consequently it can be shown that in the presence of recurrent malaria the macrophage content of these organs is enormously increased whilst the phagocytic activity of the cells is heightened to an amazing degree The source of the macrophages is still uncertain, but it is probable that they are derived from cells of the lymphocyte series

It may be argued that if immunity to malaria were based on the cellular responses already described, a general resistance to heterologous plasmodial species and strains would result, but it has been shown that unmodified infections may develop in the presence of an hypertrophied macrophage system That is to say, a highly hypertrophied macrophage system is a relatively ineffective defence against malaria in the absence of specific sensitization of the macrophages It becomes evident, therefore, that immunity to malaria is of a highly specific character which must necessarily be conditioned by specific antibodies, probably of the nature of opsonins

It is believed that these antibodies are elaborated in organs such as the liver and spleen and for this reason their presence in the peripheral blood has never been successfully demonstrated

PATHOLOGY

The pathological changes encountered in both acute and chronic malaria are largely conditioned by the destruction of the red blood cells on the one hand, and by a vigorous proliferation of the macrophages (reticulo-endothelial cells) on the other

The reduction in the red cell content of the blood that accompanies all plasmodial infections leads in time to a compensatory hypertrophy of the red bone marrow, whilst the proliferation of the macrophages is reflected in various organs but more especially in the spleen and placenta

At the same time the pigmentary deposits which accompany the intracorpuscular development of the plasmodium constitute a characteristic feature of the histopathology of those organs in which active phagocytosis predominates, whilst various non specific changes are brought about by the intense malarial toxaemia

THE SPLEEN

In acute malaria the spleen is moderately enlarged, is soft in consistency and is usually a slaty grey or black colour The distended state of the organ is reflected in the tense capsule which encloses a soft, almost diffluent, dark pulp, and is easily torn at post mortem examination Histologically the splenic pulp is diffusely congested and oedematous and shows scattered foci of haemorrhage In the case of subtertian infections the splenic sinuses commonly contain vast numbers of sporulating plasmodia Malarial pigment (haemozoin) is readily demonstrated in the form of small compact deposits which have been taken up by the splenic macrophages

It will usually be noted that if pigmentation of the malpighian corpuscles occurs at all it does so to a very limited extent

A somewhat different picture is presented by the spleen in recurrent malaria It is usually considerably enlarged, and in some cases may occupy the whole of the left hypochondrium On the other hand, in long standing chronic malaria with stabilisation of the fibrotic changes within the splenic substance, only moderate degrees of splenomegaly are observed

The organ is firm and hyperplastic while the capsule is usually thickened and at the same time shows patches of chronic perisplenitis and areas of perisplenic adhesions

The pigmentary content of the spleen in such circumstances is variable, but is always densest after a recently imposed acute attack Consequently the colour of the spleen may vary from a slate grey to black

On section, the splenic pulp is seen to be traversed by prominent white trabeculae, and on histological examination a significant hyperplasia of the macrophage cells is usually evident The malpighian corpuscles are usually small and atrophied

In this state the spleen is easily ruptured

THE LIVER

In acute malaria the liver is moderately enlarged and deeply congested The colour, however, will be determined by the extent of the pigmentary deposits and the associated degenerative changes in the hepatic parenchyma, but is commonly plum-coloured when first exposed

In subtertian infections the sinusoids are distended with heavy concentrations of parasitized red cells together with actively phagocytic macrophages In these circumstances the pressure may be such as to set up atrophic changes in the adjoining trabeculae In this way small foci of parenchymatous degeneration are brought about

Alternatively thrombotic reactions in the radicles of the portal vein in the presence of massive infections may cause areas of necrosis

Focal haemorrhages, fatty degeneration and other toxic changes may all be demonstrated In acute infections malarial pigment appears within the macrophages of the hepatic sinusoids when not contained in the parasitised red cells, whereas in chronic infections the pigment is usually distributed throughout the fibrous tissue of the portal tracts It is never found within the parenchymatous cells of the liver

While a *fine intercellular fibrosis may possibly be ascribed to* chronic malaria it is unlikely that gross hepatic cirrhosis ever occurs

THE BONE MARROW

The continued blood destruction in malaria leads to a compensatory hyperplasia of the red bone marrow which gradually encroaches and may to a variable extent replace the yellow marrow of the long bones The new erythroblastic tissue is essentially normoblastic in type although excessive stimulation may lead to a relative increase in megaloblasts The extent of the normoblastic hypertrophy is directly related to the duration and severity of blood destruction, hence the degree of reticulation that follows elimination of the plasmodial infection constitutes a measure of erythroblastic hypertrophy

A striking feature of all marrow preparations in malaria is the *great increase that takes place in the concentration of macrophages* and the vigour and scope of their phagocytic activities They can readily be demonstrated containing plasmodia, pigment, parasitised and non parasitised cells and sometimes even leucocytes In this way the bone marrow constitutes an important defence mechanism in malaria

THE KIDNEYS

A certain amount of transient renal damage occurs in the course of an acute malarial paroxysm as in any other acute febrile condition

In some instances, however, more especially in subtertian and in quartan infections, lesions of a more permanent nature may be produced

In severe subtertian infections the renal capillaries may be blocked with masses of parasitised red cells, thereby giving rise to small renal infarcts At the same time glomerular congestion, oedema of the interstitial tissue, desquamation of the tubular epithelium with focal haemorrhages and areas of necrosis may all occur in varying degrees of intensity Pigment granules appear within the vascular endothelium and in the interstitial tissue

In rare instances an acute haemorrhagic nephritis has been pre cipitated by an acute subtertian infection Nephrosis is especially common in relation to foci of quartan malaria, where it frequently becomes a feature of long standing chronic infections Although Giglioli considers that a condition analogous to chronic Bright's disease may be conditioned by chronic quartan infection, it appears to be more usual for the albuminuria to clear up after elimination of the plasmodial infection

THE SUPRARENAL GLANDS

Microscopically there is an evident loss of the normal yellow colour due to the disappearance of the fat and lipoid content of the gland

Histologically a relative or complete absence of cell chromaffin occurs in many cases whilst other changes met with include focal haemorrhages, capillary thrombosis and focal tissue necrosis These acute lesions are especially associated with subtertian infections, where it is believed they give rise to a state of vasomotor asthenia

THE PANCREAS

A condition of acute haemorrhagic pancreatitis has been described in relation to acute subtertian malaria, but the more usual changes consist in the concentration of plasmodia within the pancreatic capillaries with the production of focal haemorrhages or thromboses

In rare instances lesions of the islet tissue have been described and have been held responsible for the occurrence of a diabetic syndrome in malaria Normally, however, the degree of pancreatic involvement in plasmodial infections is insufficient to give rise to any regional clinical features

THE GASTRO-INTESTINAL TRACT

A state of diffuse gastritis is usually demonstrable in acute malaria, together with focal haemorrhages or capillary thrombosis These changes are especially common in acute subtertian infections when local tissue anoxia occurs as a sequel to the overcrowding of the gastro-intestinal capillaries by masses of sporulating plasmodia

When similar lesions develop in the large bowel, an acute diarrhoeic or dysenteric state may arise with blood and mucus in the stools In such circumstances, however, the more usual bacterial or parasitic causes of dysentery must be carefully eliminated

Finally, a pigmented atrophy of the small bowel has been described by Rogers, in which the bowel mucosa assumes a dark colour while fibrous tissue replacement of the normal bowel structure occurs

THE HEART

Severe myocardial changes are infrequent in all save severe subtertian infections either in the acute or chronic phase

When widespread sporulation occurs within the cardiac capillaries, a state of diffuse fatty change is induced which renders the myocardium pale and flabby In the same way thrombosis of the capillaries may arise with the formation of foci of cardiac ischaemia

Punctate haemorrhages, either subpericardial or subendocardial, are readily demonstrable in severe acute malaria, when they are usually associated with focal haemorrhages in the substance of the myocardium

These myocardial changes in acute malaria are reflected in a state of arterial hypotension with a tendency to acute myocardial failure in the presence of massive infections

THE LUNGS

Pulmonary changes are usually restricted to an acute congestion of the alveolar capillaries together with a variable degree of congestion of the bronchial mucosa

In some instances small intra alveolar haemorrhages may occur, usually in the lower lobes posteriorly where small areas of oedema *or alveolar collapse may be found There is no convincing evidence,* however, that plasmodial infections bring about extensive pneumonic

consolidation of the lung, even though plasmodia may sometimes be noted within the alveolar capillaries

THE BRAIN AND MENINGES

Demonstrable changes in the central nervous system are mainly confined to subtertian infections of great severity in which clinical evidence of cerebral involvement has been observed While a true malarial meningitis has been described (Laveran), the usual meningeal change consists in diffuse congestion and oedema induced by a massive plasmodial infection of the meningeal capillaries

The cerebral lesions, on the other hand, are the product of two primary factors

1 Mechanical blocking of the cerebral capillaries by masses of parasitised red cells, leading to (*a*) thrombosis, and (*b*) haemorrhage, and

2 Malarial toxaemia

The blockage of the cerebral capillaries may constitute the origin of the so-called ' malarial granulomata ' which are distributed mainly in the subcortical zones Interference with the capillary circulation leads to the formation of a small necrotic area around which small haemorrhages develop, and in due course the disintegrated cerebral substance is replaced by neuroglial elements which constitute the histological basis of a 'malarial granuloma ''

Cerebral granulomata have also been observed in the general paralytics treated by means of induced malaria In these circumstances the lesions consist in a localised proliferation of the regional macrophage cells

In the presence of severe toxaemia, the tissue changes encountered are non specific in character, and for the most part consist in numerous punctate haemorrhages scattered throughout the brain substance in conjunction with degenerative changes in the nerve cells

THE PLACENTA

A histological study of the placenta in malaria reveals two characteristic features

1 A heavy concentration of plasmodia in the intervillous spaces

2 A remarkable accumulation of actively phagocytic macrophages

THE GASTRO-INTESTINAL TRACT

A state of diffuse gastritis is usually demonstrable in acute malaria, together with focal haemorrhages or capillary thrombosis These changes are especially common in acute subtertian infections when local tissue anoxia occurs as a sequel to the overcrowding of the gastro intestinal capillaries by masses of sporulating plasmodia

When similar lesions develop in the large bowel, an acute diarrhoeic or dysenteric state may arise with blood and mucus in the stools *In such circumstances, however, the more usual bacterial* or parasitic causes of dysentery must be carefully eliminated

Finally, a pigmented atrophy of the small bowel has been described by Rogers, in which the bowel mucosa assumes a dark colour while fibrous tissue replacement of the normal bowel structure occurs

THE HEART

Severe myocardial changes are infrequent in all save severe subtertian infections either in the acute or chronic phase

When widespread sporulation occurs within the cardiac capillaries, a state of diffuse fatty change is induced which renders the myocardium pale and flabby In the same way thrombosis of the capillaries may arise with the formation of foci of cardiac ischaemia

Punctate haemorrhages, either subpericardial or subendocardial, *are readily demonstrable in severe acute malaria*, when they are usually associated with focal haemorrhages in the substance of the myocardium

These myocardial changes in acute malaria are reflected in a state of arterial hypotension with a tendency to acute myocardial failure in the presence of massive infections

THE LUNGS

Pulmonary changes are usually restricted to an acute congestion of the alveolar capillaries together with a variable degree of congestion of the bronchial mucosa

In some instances small intra-alveolar haemorrhages may occur, usually in the lower lobes posteriorly where small areas of oedema or alveolar collapse may be found *There is no convincing evidence*, however, that plasmodial infections bring about extensive pneumonic

consolidation of the lung, even though plasmodia may sometimes be noted within the alveolar capillaries

THE BRAIN AND MENINGES

Demonstrable changes in the central nervous system are mainly confined to subtertian infections of great severity in which clinical evidence of cerebral involvement has been observed. While a true malarial meningitis has been described (Laveran), the usual meningeal change consists in diffuse congestion and oedema induced by a massive plasmodial infection of the meningeal capillaries

The cerebral lesions, on the other hand, are the product of two primary factors

1 Mechanical blocking of the cerebral capillaries by masses of parasitised red cells, leading to (a) thrombosis, and (b) haemorrhage, and

2 Malarial toxaemia

The blockage of the cerebral capillaries may constitute the origin of the so-called "malarial granulomata" which are distributed mainly in the subcortical zones Interference with the capillary circulation leads to the formation of a small necrotic area around which small haemorrhages develop, and in due course the disintegrated cerebral substance is replaced by neuroglial elements which constitute the histological basis of a "malarial granuloma"

Cerebral granulomata have also been observed in the general paralytics treated by means of induced malaria In these circumstances the lesions consist in a localised proliferation of the regional macrophage cells

In the presence of severe toxaemia, the tissue changes encountered are non specific in character, and for the most part consist in numerous punctate haemorrhages scattered throughout the brain substance in conjunction with degenerative changes in the nerve cells

THE PLACENTA

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1 A heavy concentration of plasmodia in the intervillous spaces,

2 A remarkable accumulation of actively phagocytic macrophages

The features are seen to best advantage in infections with *Pl falciparum*

The intervillous spaces are crowded with compact trophozoites and maturing schizonts, many of the red corpuscles show multiple infections, but ring forms are scanty and gametocytes are rarely or never found The heavy concentration of parasites in this situation is probably due to the sluggish circulation in the sinuses where reproduction by schizogony goes on steadily with only a small percentage of parasites reaching the general maternal circulation

For this reason plasmodia will always be more readily demonstrated in placental smears than in blood films prepared from the peripheral blood

The macrophage response to plasmodial infections is also strikingly seen in relation to the intervillous spaces, which in normal circumstances contain nothing but blood In established or relapsing malaria many of these spaces are virtually obliterated by masses of macrophage cells and in some cases they may be so numerous as to jeopardise the foetal circulation It has even been suggested that abortions in malaria may sometimes be due to physical rather than to toxaemic causes

The vigorous phagocytosis that takes place in the placenta is largely the monopoly of the macrophages, although there are other cells that may play a minor role Histologically, therefore, the placenta clearly shares in the defence against malaria, and it is thought that in hyperendemic areas it may be indirectly responsible for the low parasite rate in infants up to two months

CHAPTER FOUR

CLINICAL FEATURES

When acute malaria is regarded from the strictly clinical view point, it tends to fall into two categories In the one, the paroxysms are sharp and severe but grave complications are rarely or never encountered, whereas in the other, not only is the febrile paroxysm severe, but there is an ever present risk of serious complications arising Hence on clinical grounds acute malaria may be grouped as (1) acute benign malaria, and (2) acute malignant malaria From the parasitological view point the benign forms are due mainly to *Pl vivax*, *Pl ovale* and *Pl malariae*, while the malignant forms are associated with infections with *Pl falciparum*

The clinical features of malaria may be still further modified (*a*) in terms of a frequently recurring attack, and (*b*) in terms of racial immunity In both circumstances a state of chronic malaria is induced which, however, varies as between the European and indigenous races

The following clinical classification will be adopted in the present discussion

Malaria in the European

1 Acute benign malaria
2 Acute malignant malaria
3 Chronic malaria

Malaria in the African

1 Acute malaria
2 Chronic malaria

MALARIA IN THE EUROPEAN

1 ACUTE BENIGN MALARIA

This variety of acute malaria constitutes the clinical expression of infection with *Pl vivax*, *Pl ovale* or *Pl malariae* The febrile paroxysms, though severe enough in themselves, are seldom accompanied

by the onset of pernicious symptoms Exceptions to this rule undoubtedly occur, as, for example in the case of the cerebral attacks induced by *Pl vivax* infections in Macedonia during the last war, but such exceptions are rare

Again while renal complications may arise in the course of an uncontrolled quartan infection, the tendency for the renal lesions to resolve in the presence of adequate anti plasmodial therapy renders it unnecessary to regard this as a "malignant" complication

Finally, in *Pl ovale* infections the febrile paroxysms are usually shorter and milder than in the other forms, so that far reaching constitutional disorders are relatively infrequent in this type of infection

INCUBATION PERIOD

The average incubation period in *Pl vivax* and *Pl ovale* infections varies from 10 to 20 days and represents the interval that elapses between the inoculation of the sporozoites by the mosquito and the first febrile paroxysm This period may be very materially modified either by quinine or mepacrine prophylaxis or by some measure of natural immunity For these various reasons the incubation period, or perhaps more strictly the period of latency, may last for several months or even extend over a year

This phenomenon is especially common in *Pl vivax* malaria in temperate zones where infections acquired in the summer or autumn months may not become clinically apparent until the following spring

In *Pl malariae* infections the average incubation period ranges from 12 to 21 days, but it is especially noteworthy that the parasite may remain dormant for years

PRODROMAL SYMPTOMS

The actual malarial paroxysm is sometimes preceded by certain premonitory symptoms which include a feeling of tiredness in association with recurrent chilly sensations, headache, anorexia, pains in the bones, stiffness in the neck muscles and fugitive fluctuations in temperature

THE FEBRILE PAROXYSM

The actual febrile paroxysm sets in abruptly with a violent rigor and the subjective sensation of intense cold This marks the beginning

of the cold or shivering stage which may last from 30 minutes up to about two hours The patient looks pinched and cold and the whole body shivers violently and uncontrollably, so that his teeth chatter audibly, his speech becomes jerky and uncertain and he vainly attempts to get warm by piling on blankets and surrounding himself with hot water bottles, even though the weather be sweltering hot

Even at this stage of the attack the temperature has begun to rise and may soon reach 100° to 102° F Frontal headache sets in early in the attack and may be severe Sometimes it culminates in and is partially relieved by a sharp epistaxis Nausea and vomiting are common and in some cases the paroxysm may be initiated by violent vomiting The pulse is rapid and usually of low tension

Then in due course the clinical picture changes abruptly as the cold stage merges rapidly into the hot or febrile stage During the transition stage the patient may experience a fleeting sense of well being, but soon becomes so hot and uncomfortable that he rapidly casts aside his bed clothes

The skin is now hot and dry the face flushed and the headache increases in intensity as the temperature rises to about 105° F Myalgic pains develop all over the body, but are especially acute in the lumbar region The vomiting becomes more urgent as the pyrexial phase develops, the respirations quicken and the pulse is now full and bounding The tongue becomes dry and furred and the conjunctivae congested Meanwhile the patient feels and looks acutely ill, and there is frequently a tendency to delirium at the height of the pyrexial phase

After a period of from one to six hours the dry burning pyrexia gives way to the stage of sweating The break in the pyrexia is heralded by the appearance of a few beads of sweat on the forehead near the hair margin, and then very soon the whole body is drenched in a soaking sweat which continues to pour from the body for the next two to four hours

The temperature falls by crisis with the onset of profuse sweating, and a feeling of relief and comfort replaces the misery and distress of the dry pyrexia As the sweating passes off, the patient rapidly recovers his sense of well being and may either doze off into a restful sleep or may enjoy a light meal

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The whole attack will have occupied from six to ten hours

Physical signs during the paroxysm During the initial stage of shivering the skin remains cold and "blue," but with the onset of the hot stage it becomes hot, dry and flushed, and continues thus until the pyrexia breaks, when it rapidly cools in the presence of the profuse perspiration Very occasionally an erythematous rash develops during the hot stage, when it most commonly appears as a roseolar eruption As the attack develops, a slight icteric tinge appears in the skin and conjunctivae, but is more apparent in recurrent malarial attacks than in a primary paroxysm The eyes are usually bright and alert even though conjunctival congestion prevails The pulse is rapid and of low tension initially, but becomes full and bounding as the fever stage develops

The blood pressure may fall to low levels at the beginning of an attack, but in the ordinary sthenic type of malarial paroxysm it approximates to normal values during the hot stage

Signs of a mild bronchitis are frequently apparent, although the persistent dry cough may be the result of a mild tracheitis, in which case no particular chest signs will be noted The tongue soon becomes coated and the bowels may either be loose or constipated

The spleen undergoes progressive enlargement during an attack but may not be palpable until after a series of paroxysms have occurred, nevertheless, some degree of splenic tenderness can practically always be elicited on deep and steady palpation in the left hypochondrium, even in the absence of demonstrable splenomegaly

A moderate degree of hepatomegaly frequently occurs, but even though this feature may not be particularly noticeable, hepatic tenderness is almost invariably present

Labial herpes commonly develop early in an attack of acute benign malaria, but the mouth, face and ears may also be involved

During the cold stage the urine is pale in colour and of low specific gravity, but with the onset of the hot phase it becomes concentrated and highly pigmented by reason of the high urobilin content Febrile albuminuria is the rule, while in quartan infections a true malarial nephritis may supervene

The cytological and chemical changes that take place in the blood during an acute attack of malaria have already been described

COURSE OF THE DISEASE THE TEMPERATURE CHARTS

The "classical" temperature chart in acute benign malaria is characterised by a recurring series of pyrexial paroxysms consisting of an abrupt rise, a sharp peak reaching 104° to 105° F, a steep fall and a narrow base In the case of *Pl vivax* and *Pl ovale* infections, the febrile paroxysm recurs every third day, and in the case of *Pl malariae* infections every fourth day Between the paroxysms the temperature remains at normal or subnormal levels, and in the absence of treatment a sharp recurring pyrexial reaction will persist with either a tertian or a quartan periodicity over a period varying from a few days to one or two months

The "classical" temperature is not always observed in benign malaria Thus a quotidian type of fever may be encountered during the first few days of the attack, to be followed later by a true tertian or quartan periodicity Sometimes the opposite state of affairs obtains The explanation lies in the existence of two generations of plasmodia developing in series and so precipitating a quotidian fever The disappearance of one generation in the course of an attack or its tendency to assert itself later in the attack will be the determining factor in the timing of a true tertian or quartan periodicity

The pyrexial paroxysm tends to occur with greatest frequency between midnight and noon except in infections with *Pl ovale*, when the rise of temperature takes place in the late afternoon or at night

UNTREATED BENIGN MALARIA



and is apparently maintained at an effective level so long as the plasmodium persists as a subclinical infection There is, however, an ever present tendency to relapse, especially in the presence of some debilitating factor such as chill, fatigue, intercurrent disease and so on On the other hand, a relapse may occur in the absence of any demonstrable precipitating cause

Clinically a relapse consists in a sharp febrile paroxysm which presents all the features of a primary attack, although usually in lesser degree The periodicity, either tertian or quartan, is main-

myalgic pains which attain their greatest intensity in the lumbar region

Vomiting sets in early in the attack and may be of such severity as to give rise to great prostration and exhaustion

Delirium is common at the height of the attack

The pyrexial phase is usually prolonged from 12 to 18 hours, but the subdivision of the attack into relatively short, sharply defined cold, hot and sweating stages is rarely observed The patient remains in a state of hot, dry pyrexia throughout the attack and only obtains relief from his distress with the onset of sweating As in the benign forms, the sweating is profuse and is an essential prelude to a brief apyrexial period

Physical Features of the Attack The skin remains hot, dry and burning throughout the paroxysm, while the face looks flushed and the eyes congested The patient is very obviously acutely ill The prostration which is usually associated with acute malignant malaria is always sharply accentuated by severe and persistent vomiting Hence in such circumstances the blood pressure remains low and the pulse soft and rapid

A fleeting exanthem may be observed at the onset of the attack
The pyrex usually of the roseolar type, but in some very acute infections
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COURSE OF THE DISEASE TEMPERATURE

Temperature curves in *Pl falciparum* infection reveal an essentially quotidian periodicity in which the temperature rises less ly than in the benign forms The stage of pyrexia is more ted and is characterised by the presence of remissions before

the final fall to normality In these circumstances a four hourly temperature chart shows several sharp peaks *in the course of a single* febrile paroxysm The apyrexial interval is brief However, it must be emphasised that a wide range of temperatures is encountered in acute malignant malaria In some cases the temperature rises in a step ladder fashion as in the opening phases of typhoid fever, at other times an approximately tertian periodicity is observed, or the paroxysms may run into one another with the production of a remittent fever

It is therefore wiser to be without any rigid concept of the pyrexial pattern in acute malignant malaria

THE UNTREATED ATTACK OF MALIGNANT MALARIA

A study of the natural history of untreated (or imperfectly treated) malignant malaria at once reveals its potentialities for grave and often rapidly fatal complications, and it is in this important respect that acute malignant malaria differs so fundamentally from the benign form The biological background to this differentiation is to be found in the sporulation of *Pl falciparum* within the capillaries of the internal organs such as the brain, heart and adrenals, thereby inducing serious and even fatal structural or functional damage It follows, therefore, that in the absence of treatment a heavy infection with *Pl falciparum* will almost inevitably move rapidly to a *fatal termination, probably within the space of 24 hours, certainly* within a few days

In less massive infections in which the body is given time to mobilise its cellular and humoral defences, the temperature gradually subsides after a week or two of daily paroxysms and an afebrile period lasting perhaps 10 to 14 days will ensue

From now on relapses occur, and although they may be milder than the original attack it is always possible for the course of the disease to be abruptly interrupted by fatal involvement of a vital organ More often, however, the relapses grow less frequent and less severe until after about 12 to 18 months they may disappear altogether

PERNICIOUS FORMS OF ACUTE MALIGNANT MALARIA

It has already been mentioned that the intensive sporulation of *Pl falciparum* within the capillaries of the internal organs constitutes

the main biological basis of the grave clinical variants encountered in acute malignant malaria. This phenomenon, peculiar to *Pl falciparum*, leads to extensive capillary blockage which, together with the associated toxaemia must necessarily have serious clinical implications when vital organs such as the brain, heart or adrenals constitute the main focus of infection

These grave or pernicious forms are encountered most frequently amongst Europeans and especially amongst non immunes such as newcomers or young children in an area of endemic or hyperendemic malaria in which *Pl falciparum* constitutes the dominant plasmodial species On the other hand Europeans who have already suffered from malignant malaria may succumb to one of the pernicious forms, either in the presence of a massive infection or by reason of inefficient therapy A state of general debility induced by pre-existing disease or malnutrition and the absence of a spleen will still further pre-dispose the European patient to the grave forms of malignant malaria

As will be seen later, pernicious forms are rarely encountered in the African, except in the case of African infants in whom cerebral malaria is a frequent cause of death

The clinical manifestations of the pernicious forms are many and varied, and on analysis it will usually be found that the clinical pattern in any given case is determined by two primary factors —

1 The anatomical site of the massive internal sporulation and

2 The profound toxaemia occurring in association with the developmental cycle

Consequently, apart from exhibiting characteristic features, the patient is always acutely ill in the pernicious forms of acute malignant malaria

It is undoubtedly the case that this type of malaria may simulate almost any acute febrile disease, whether medical or surgical hence apart from being conversant with the common clinical variants of pernicious malaria, it is highly important to exclude the disease in any acute febrile illness in which the diagnosis may be in doubt This is especially important in surgical practice

The pernicious forms of malignant malaria fall into fairly well defined clinical types, the main varieties of which will be discussed in series

ALGID FORMS

The dominant clinical feature in algid malaria is the overall state of collapse, and as this is the one form of malaria in which there may be no rise of temperature, it must always be kept in mind if a serious diagnostic error is to be avoided

The patient is pallid and collapsed with a thin thready pulse and a cold clammy skin The breathing is shallow and rapid and weakness is extreme, while nausea and vomiting with cramps in the leg muscles commonly occur *The temperature of the body surface is always* subnormal, but the rectal and oral temperature may be in the neighbourhood of 99° or 100° F

The clinical state is clearly a reflection of the intense vasomotor collapse which prevails and is thought to imply a massive infiltration of the adrenal glands by sporulating plasmodia

A similar clinical picture results from a heavy invasion of the myocardium In these circumstances the temperature falls and restlessness sets in Dull pain over the precordium is usually complained of, and on examination the heart sounds will be soft and remote while some variety of arrhythmia may set in

The cardiovascular changes in algid malaria may be compared with those encountered in diphtheria in that the symptom complex may be conditioned by

1 Paresis of the peripheral vasomotor system, or
2 Direct involvement of the myocardium

Whatever the precise pathological basis of the algid state in malaria may be, the situation is an extremely dangerous one with a tendency *to terminate fatally unless recognised promptly and treated expeditiously*

CEREBRAL FORMS (CEREBRAL MALARIA)

Cerebral malaria constitutes one of the gravest forms of acute malignant malaria It occurs most frequently in infants and young children, both African and European, and in non-immune newcomers to any area in which *Pl falciparum* infections predominate

An attack is precipitated by the sudden massing of sporulating plasmodia within the capillary vessels of the brain and meninges

The pathological reactions that occur in these circumstances have already been described, and on the basis of these reactions

CLINICAL FEATURES

the clinical features of cerebral malaria may be grouped in two categories —

1 The meningeal form in which the infection is concentrated in the meningeal vessels, and

2 The encephalitic forms in which sporulation occurs mainly within the brain substance, either in a focal or in a diffuse manner

It must be appreciated, however, that cases presenting evidence of simultaneous involvement of both the meninges and brain substance are also met with, but as a rule in any given case either the meningeal or the encephalitic element predominates

MENINGEAL FORMS

These forms are not encountered very frequently, but when they do occur they present all the clinical features of meningeal irritation with intense headache, pains in the back and legs, vomiting and stiffness of the neck muscles with some degree of head retraction

The temperature is practically always continuously high, remaining between 104° and 105° F

On lumbar puncture a considerable increase in the pressure of the cerebrospinal fluid will be found, but it is unusual to find any chemical or cytological abnormalities Very occasionally a mild pleocytosis may occur

Since the meningeal reaction is of an acute nature accompanied by severe toxaemia, the tendency is for fatal coma to set in rapidly in the absence of speedy and effective therapy

ENCEPHALITIC FORMS

Cerebral malaria expresses itself with greatest frequency in one of the encephalitic forms, but in view of the fortuitous distribution of the plasmodia within the brain substance a wide range of clinical types is encountered

General Syndromes When the plasmodia are distributed diffusely throughout the brain substance or when a state of profound toxaemia prevails, a fairly well-defined symptom complex sets in consisting essentially of an ingravescent coma

The patient becomes drowsy, apathetic and non-cooperative He resents being examined and usually lies with his eyes closed, either because of the drowsiness or on account of photophobia There is

a generalised slackness of the muscles with diminution or loss of reflexes

The temperature rises to 104° or 105° F, but rarely exceeds 106° F

As the attack develops a general restlessness sets in often accompanied by the onset of jerky movements of the limb and face muscles In children convulsions frequently occur at this stage, either as an isolated event or as a series of attacks

Mental confusion is now apparent as the patient lapses into a state of semi-consciousness Finally, complete loss of consciousness follows, when the patient may be either delirious or in a deep coma

Muscle twitchings frequently persist into this stage, with or without generalised convulsions, and in the event of a spread of the infection to the meninges, head retraction with spasm of the trunk muscles may be superimposed on the original clinical picture

As the attack moves swiftly to its close, the twitchings and convulsions cease, and a state of deep coma prevails At this stage nothing can avert a fatal issue The march of symptoms may take place with alarming rapidity, so that a child taken ill in the morning may be dead by evening In fulminating cases of this type the attack sets in with a violent convulsion or series of convulsions to be

fulminating cases of cerebral malaria a delay of more than 12 hours from the onset of the attack to the start of treatment will seriously prejudice the patient's chances of recovery

In other cases the encephalitic syndrome is dominated by a state of cerebral excitation The degree of excitement varies from excited, ceaseless talk to one of extreme restlessness and even mania A high temperature persists throughout the attack

In the absence of specific therapy, excitement gives way to coma and death

2 *Local Syndromes* When plasmodial invasion of the brain substance evolves as a focal rather than a diffuse lesion, a wide range of local neurological syndromes may be encountered

These include hemiplegia, monoplegias, aphasia, diplopia, signs of bulbar paralysis, Jacksonian epilepsy and so on On rare occasions involvement of the spinal cord occurs with the production of para-

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It is more usual, however, for the attack to evolve more gradually over a period of 24 to 48 hours, but even in what may be called non fulminating cases of cerebral malaria a delay of more than 12 hours from the onset of the attack to the start of treatment will seriously prejudice the patient's chances of recovery

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rashes are only found in the presence of a profound malarial toxaemia

In some cases, and for the same reason, profuse bleeding takes place from the nose, mouth, gastro-intestinal tract, lungs or genito-urinary tract

3 CHRONIC MALARIA

In the presence of repeated or inadequately treated attacks of malaria a clinical state is gradually evolved, to which the term chronic malaria is applied The period of time required for the production of this chronic state is necessarily a variable quantity, but even in the presence of constant reinfection a period of about a twelve-month will usually elapse before chronicity may be said to have established itself

The condition implies the persistence of the plasmodium in the tissues of the human host not in a state of commensalism but as a true pathogen, whose activities have been modified by virtue of prior activation of the immunity mechanism both in respect of its humoral and cellular components In this way the clinical responses to the plasmodial infection no longer assume the acute overtly febrile character of a primary infection, but are "damped down" to the extent of giving rise to a complex syndrome which may be said to represent the sum of a modified malaria toxaemia and a progressive malarial anaemia While the syndrome of chronic malaria may be summarised in terms of this apparently simple formula, its complexity is such that it has become a favourite clinical scrap-heap for conditions difficult of accurate identification

The basic criteria on which the diagnosis of chronic malaria must depend are dealt with later in the section on diagnosis, meanwhile the main clinical features of the condition will be discussed

The clinical pattern varies considerably in degree, hence the following description may be said to represent the findings in a typical case of chronic malaria in the European, but it must be remembered that mild clinical variants exist and may prove more difficult of recognition

CLINICAL FEATURES

The salient feature of chronic malaria is a state of general debility which is characterised by persistent lassitude in both a physical

and a psychological sense That is to say, the patient is always tired so that *his* capacity for any sustained mental or physical effort is grievously impaired Consequently he shows an increasing tendency to shirk the daily routine Then too the discovery that he can no longer concentrate nor remember things easily exercises a depressant effect on his general outlook and gives rise to a weariness of the spirit and even a sense of hopeless frustration

Anorexia is common and is frequently accompanied by feelings of nausea and even a tendency to vomit occasionally, especially immediately after a meal This feature is probably related to the state of chronic catarrhal gastritis which supervenes on the associated achlorhydria or hypochlorhydria The poor appetite leads in turn to loss of weight, so that in a well-established chronic malaria the patient is constantly underweight to the extent of emaciation in the more severe cases Constipation is usual, but a spurious diarrhoea may occur from time to time, either by reason of the defective gastric secretion or on account of recurrent infections of the vulnerable gastro-intestine

Headache is a frequent complaint and is often of maximal intensity in the lower occipital region It may also show a tendency to develop at a more or less regular time each day, and is seldom relieved except to a limited extent by ordinary headache tablets, whereas antimalarial therapy is invariably effective In some cases the headache assumes the characteristics of a hemicrania

A state of vasomotor asthenia is common and is characterised by arterial hypotension in association with poor myocardial tone, shortness of breath even on moderate exertion, and in some cases hypostatic oedema may be found

Sweating with subjective shivering sensations occur from time to time, and may even show a rough periodicity

Apart from general dulling of the mental processes already mentioned, certain psychotic disorders may arise in previously normal individuals A bright, cheerful personality may give way to general apathy and depression, which merges eventually into a state of melancholia There may even be attacks of disorientation or clouding of consciousness after which the patient may have no recollection of his activities Alternatively curious aberrations of conduct may occur in which the patient becomes unexpectedly irritable and unreliable

During these phases he is often untruthful in a petty stupid way and may abandon any sense of responsibility in regard to the execution of his routine duties

In some cases the presenting symptoms may be of a neurological character such as neuritis of a cranial or a peripheral nerve, e g, the fifth cranial nerve or the sciatic nerve In such cases the neuritic symptoms tend to appear and disappear in an irregularly periodic manner

Finally, the granulomatous and sclerotic lesions which follow in the wake of cerebral malaria may be responsible for a variety of chronic neurological syndromes ranging from disturbances of speech to spastic paraplegia

PHYSICAL SIGNS

In a well-established case of chronic malaria the patient looks tired and thin, and may even have a cachectic appearance The skin and sclerae show a distinct yellowish tinge which accentuates still more his sickly appearance

The spleen is usually palpable but the degree of enlargement varies from case to case The spleen is not usually tender, but a dragging pain or ache in the left hypochondrium is often enough complained of, and can probably be explained in terms of a chronic perisplenitis or chronic perisplenic adhesions The spleen in chronic malaria is always firm, even hard, and is easily traumatised

A moderate degree of hepatomegaly usually develops but no textural changes occur

The blood pressure tends to be low in conformity with the general vasomotor hypotension, whilst the cardiac tone is poor Periodic attacks of tachycardia are frequently encountered, and in the presence of severe anaemia haemic murmurs are heard The haematological changes have already been discussed, but may be summarised by saying anaemia of varying degree is encountered

The urine is usually highly coloured, largely on account of an increase of urobilin excretion, whilst traces of albumin are common

When the temperature is taken systematically, a low continuous fever is the rule with periodic rises to 100° F or so, lasting only an hour or two at the most. These periodic febrile reactions are usually accompanied by sensations of cold or an attack of sweating, or by exacerbation of the presenting clinical feature

Finally, in the case of chronic malaria becoming established in a European child from an early age, a state of infantilism may be induced

MALARIA IN THE AFRICAN

From infancy onwards the African of the kraals is exposed to repeated plasmodial infection The mortality rate is necessarily high, but those who survive gradually build up a considerable measure of immunity despite such debilitating factors as malnutrition, polyparasitism and general poverty

Except in very young children malaria is therefore a relatively mild disease in the African, so that clinically it may be grouped as

1 Acute malaria,
2 Chronic malaria

This grouping applies, whatever the causal parasite, which in any given case can be determined by blood smear examination only Very occasionally, in the case of *Pl falciparum* infections, pernicious complications occur, either on account of a massive infection or as a sequel to depression of the premunity in the presence of general debility

ACUTE MALARIA

This is predominantly a disease of infants and young children in whom premunition has not yet been established Consequently the clinical features are essentially the same as those encountered in the non immune European and have already been described Furthermore, in the case of *Pl falciparum* infections, pernicious complications, including cerebral malaria, occur and account for a considerable proportion of deaths amongst African infants

In older children and adults living in an endemic area, the gradual *acquisition of a relative immunity to plasmodial infections becomes* evident in the clinical features of the malarial attack The rise of temperature which heralds the onset of a paroxysm is seldom accompanied by shivering, and the actual rise of temperature is less and of shorter duration than in the European Headache and diffuse myalgic pains, though not severe, are common features of an attack, but both vomiting and sweating are usually absent A troublesome cough is not uncommon

Complications are practically unknown in the immune African except in quartan malaria, in which malarial nephritis not infrequently occurs

Very rarely an acute malarial attack is complicated by the onset of cerebral malaria, or even blackwater fever

Finally, all cases, whether complicated or not, show a rapid response to quinine or mepacrine therapy, although spontaneous recovery will usually take place in the absence of plasmocidal drugs

CHRONIC MALARIA

In the majority of cases chronic malaria exists in the African without giving rise to any significant features, even though plasmodia may be present in blood smears

Thus the stigmata of ill health so well portrayed in the European in like circumstances are strikingly absent in the African

Splenomegaly is almost always present in chronic malaria, but *varies in degree In some cases the spleen extends almost to the* umbilicus whilst in others it may be barely palpable It is hard but not tender, although the presence of areas of perisplenitis is frequently associated with a dragging ache or pain in the left hypochondrium

A low grade continuous pyrexia is sometimes observed, but is seldom sufficiently pronounced to interfere with the patient s daily routine

Finally, in highly malarious areas, the blood deteriorates to a greater or less degree, so that anaemia, usually in the form of a moderate hypochromic type, becomes apparent Occasionally an anaemia of the macrocytic type is encountered, but it may be difficult to ascribe this to malaria alone The anaemic state is usually associated with anorexia and loss of weight, although never to the same extent as in the European

paroxysm, which may evolve through fairly sharply defined phases, terminating in a drenching sweat or, in the absence of such phases, headache, vomiting and backache constitute the presenting clinical features which, after some hours, are relieved by a heavy sweat

These features, together with a tender and enlarging spleen, constitute presumptive evidence of an acute malarial attack, and in the absence of laboratory facilities, would justify a course of antimalarial therapy

Wherever possible the diagnosis should be confirmed by direct examination of blood smears for plasmodia By this means not only is the diagnosis confirmed, but the species of the infecting plasmodia is identified, and if we accept the clinical classification of acute malaria into benign and malignant forms it is clear that species identification is of more than academic interest It may be said to afford information of considerable prognostic value both in an immediate and in a more remote sense

THE EXAMINATION OF BLOOD SMEARS

The preparation and examination of blood smears constitutes the basic procedure in the laboratory diagnosis of malaria, but it must never be forgotten that plasmodia will not always be demonstrable in every case of acute malaria

Wherever sporulation is occurring freely in the peripheral blood no difficulty will be experienced in demonstrating the parasites, but in the presence of chemoprophylaxis with quinine or mepacrine or when, as in the case of *Pl falciparum* infections, sporulation takes place within the capillary system of the internal organs, parasites may be extremely difficult to find in smear preparations, even during a febrile paroxysm Consequently, to enhance the accuracy of smear diagnosis in malaria, a series of preparations should be made at regular intervals, say, every two or four hours

With these limitations in mind the clinician should never be afraid to base his diagnosis of acute malaria on an accurate assessment of the clinical findings and so avoid unnecessary and even dangerous delay in the application of vigorous therapeutic measures

PREPARATION OF THE BLOOD SMEARS

Blood for the preparation of smears is most conveniently obtained from the dorsal surface of the terminal phalanx of the thumb just

behind the nail The site is cleansed with spirit and after drying is pricked with a sharp triangular needle or with a triangular splinter of glass

To prepare a thin smear, a blob of blood is expressed and a clean glass slide brought gently into contact with it so that a portion of the drop is transferred to one end of the slide This slide is then laid flat and held between the finger and thumb of the left hand A second or spreader slide is brought into contact with the drop of *blood in such a way that the blood spreads rapidly along the junction* between the two slides* The spreader slide, held at an angle of about 20°, is then pushed steadily and rapidly over the surface of the first slide, thereby leaving behind a uniform layer of blood The blood film so formed is then dried in air

A thin smear prepared in this way should be a single cell layer thick and should neither extend to the edges of the slide nor reach its distal end

As soon as the smear has been prepared the patient's name or initials should be written in the blood at one end of the film, which, if it cannot be stained immediately, must be suitably protected against flies, ants and cockroaches

Thick films should always be prepared at the same time either on the same slide, but preferably on a separate one A large drop of blood is placed on the centre of the glass slide, and using a stout

it tends to flake off the slide during drying So long as the hands of a watch can be seen through the drying drop the density of the preparation may be regarded as satisfactory It is then dried in air, preferably under a petri dish and duly labelled

FIXATION AND STAINING OF BLOOD FILMS

Thin Blood Films The Giemsa staining technique constitutes a reliable and satisfactory procedure in the examination of blood films for plasmodia The films are fixed for two or three minutes in methyl alcohol either by immersion in a specially constructed trough or by laying the glass slide film side upwards across two parallel glass

rods (fixed on plasticine across a sink) and flooding it with the fixative

Absolute or 96% alcohol may also be used, when a period of 10 to 15 minutes must be allowed for fixation

The fixative is drained off and the sl de dried in air. Thereafter it is flooded with Giemsa's solution which has been diluted in the ratio of one drop of the stain to 1 0 cc of buffer solution consisting of 1 G potassium dihydrogen phosphate and 2 G sodium phosphate (tribasic) in 1,000 cc of distilled water Staining is allowed to continue for half to three-quarters of an hour, after which the slide is held horizontally and the stain floated off by flooding with tap water The stained film is then rapidly dried in air or by placing between clean blotting paper, and is then ready to be examined

Where rapid examination of a blood film is necessary a more concentrated form of Giemsa s stain may be employed by mixing one part of Giemsa's with five parts of water and staining from five to ten minutes The stain is washed off as described, and the film dried on clean blotting paper

When Giemsa's stain is employed the nuclear chromatin of the plasmodium appears a bright red with the cytoplasm staining blue or pink The nuclei of the white cells stain dark violet, the platelets a light violet red, with the red cells a salmon pink colour

Thick Film Preparations Thick films are not fixed so that they may be stained and dehaemoglobinized simultaneously

After drying, the slide is placed on its edge in a trough containing Giemsa's solution (diluted in the ratio of one drop of the stain to 1 0 cc of buffer solution) and left standing for 30 minutes

The watery nature of the staining solution rapidly releases the haemoglobin in the preparation The slide is then dipped in a beaker of tap water and gently moved to and fro to remove all traces of stain Finally, it is dried in air

Various staining techniques have been evolved with the object of obtaining better contrasts in the stained preparations with a minimum of distortion of leucocytes and protozoa The most successful of these techniques is undoubtedly Field s thick film method, the details of which are as follows —

Preparation of the Stain

Two isotonic solutions are employed with a pH adjusted to 6 6

Solution (1)	
Methylene blue	0 8 G
Azure blue	0 5 G
Disodium hydrogen phosphate (anhydrous)	5 0 G
Potassium dihydrogen phosphate (anhydrous)	6 25 G
Distilled water	500 cc
Solution (2)	
Eosin	1 0 G
Disodium hydrogen phosphate (anyhdrous)	5 0 G
Potassium dihydrogen phosphate (anhydrous)	6 25 G
Distilled water	500 cc

These solutions are allowed to stand for 24 hours and are then filtered They keep for several weeks but may require filtering from time to time to remove any scum or any sediment that might interfere with the staining results The appearance of a greenish tinge in the eosin solution is an indication that it should be discarded

Technique and Staining

(1) Dip the film in Solution (1) for one second
(2) Rinse immediately in clear tap water until stain ceases to flow from the film
(3) Dip in Solution (2) for one second
(4) Rinse in clear water
(5) Drain and dry by placing vertically against a staining rack

Considerable experience is necessary for the accurate interpretation of thick smear preparations, whatever the staining technique may be In the case of young trophozoites the ring stage is seldom preserved but the cytoplasm stains fairly deeply except in *Pl falciparum* infections when the cytoplasm of the young rings may be very difficult to discern The chromatin appears smaller and more faintly stained than in Giemsa stained thin film preparations

Schizonts are deeply stained and therefore easily distinguished although it is sometimes difficult to distinguish the larger forms from gametocytes except in *Pl falciparum* infections The chromatin

is not well defined but the cytoplasm stains deeply and the pigment is usually in evidence

Species differentiation is therefore a matter of some difficulty, *but a consideration of such features as the size and concentration* of the parasites, the texture and arrangement of the pigment, the number of merozoites in the mature schizonts and so on, will assist in species diagnosis It will usually be found more profitable to differentiate the species in thin rather than in thick smear preparations

CHRONIC MALARIA

From the clinical viewpoint malaria in the European both in its latent and chronic forms commonly appears as an obscure illness in which a state of general debility possibly accompanied by splenomegaly constitutes the presenting clinical feature

In the case of the immune African a chronic or latent infection is usually devoid of clinical features although a palpable spleen may provide a clue to the malarial background While the patient's clinical history together with the knowledge that he resides in a known malarious area will provide presumptive evidence of chronic malaria, it is always desirable to obtain a modicum of laboratory support for the diagnosis otherwise there is a temptation to group all manner of chronic ills in this category Unfortunately the scarcity of plasmodia in the peripheral circulation renders it necessary to have recourse to indirect procedures in the laboratory diagnosis of chronic or latent malaria

HAEMATOLOGICAL FINDINGS

1 *Thick Blood Smear Preparations*

Thick smears should always be studied on the grounds that it may be possible to demonstrate either a trophozoite or perhaps a gametocyte

2 *The Pigmented Leucocyte*

While the bulk of the malarial pigment is taken up by the macrophages of the spleen, liver and bone marrow, a certain amount is sometimes to be found in the leucocytes of the peripheral blood especially in the large hyaline monocytes but sometimes in the neutrophiles

The pigment appears in the form of coarse yellowish brown or brownish black granulations and is more likely to be found in thick smear preparations than in thin films The presence of this intracellular pigment in the peripheral blood always means that the patient is infected with the malaria parasite

3 *The Differential White Cell Count*

The behaviour of the white blood cells in malaria has already been discussed While it cannot be claimed that an absolutely specific haemogram obtains in chronic malaria there are certain findings which, when taken along with the clinical data, may be said to provide presumptive evidence of the disease The total white cell count usually falls within or just below the normal range, while the percentage of monocytes increases to 15% or over

Thus the position may be summarised by saying that where chronic or latent malaria is suspected on clinical grounds a leucopenia with a relative monocytosis provides valuable support to the diagnosis and would justify a course of anti malarial therapy

SEROLOGICAL FINDINGS

1 *Henry s Serological Test*

Henry's reaction is based on the assumption that flocculation of melanin or of iron albuminate will be brought about in the presence of the serum anti bodies that develop in response to malarial pig ment

The reaction, however, is probably related to the increase in the plasma euglobulin which flocculates in the presence of distilled water

Flocculation may also be induced by lowering the pH of the plasma hence the reaction cannot be regarded as a specific serological test, but the high incidence of flocculation occurring in plasmodial infections supports the diagnostic validity of the test in the laboratory investigation of the disease

The test is positive in the majority of cases of acute and chronic malaria and although a small percentage of positives may be obtained in non malarial conditions recent improvements in technique appear to have reduced the margin of error to between 1 and 3%

The chief value of the test lies in the investigation of chronic or latent malaria, but it is clearly of little more than academic interest in acute malaria

Where a patient is suspected of suffering from chronic malaria but in whom no parasites can be found, a negative Henry's reaction may be said to exclude the disease A positive reaction on the other hand supports a diagnosis of malaria

Melano flocculation In carrying out the melano-flocculation test melanin is obtained by scraping the choroid from ox-eyes and suspending the gelatinous material in two volumes of doubly-distilled water The suspension is ground in a mortar containing fine sand and thereafter a little formaldehyde (1 in 200 solution) is added After filtration through loosely packed glass wool the filtrate is centrifuged for eight minutes at 4 000 revolutions and is then stored under sterile conditions for a month in a refrigerator

The melanin is then standardised in a series of dilutions to which 0 2 cc of test serum is added and after two and a quarter hours incubation at 37° C , a final reading is made after a further 15 minutes at room temperature Only definite large floccules are regarded as positive

Ferro-flocculation The test consists in adding 0 2 cc of serum to each of a series of test tubes containing respectively 1 in 450 methar fer, 1 in 4 800 iron albuminate, 1 in 6,000 iron albuminate with doubly distilled water as the diluent in each case The control tubes contain doubly distilled water, 1 in 4 800 iron albuminate and 1 in 1,000 saline solution

The suspensions are kept at 37° C for two and a half hours and then at room temperature for another 30 minutes, after which they are examined for flocculation

In a positive reaction large flocculi are seen

Wolff's Modification of Chorine s Technique The serum to be tested is prepared by collecting 3 0 cc of venous blood which is placed in a dry centrifuge tube until the clot has formed and loosened It is then placed in a refrigerator overnight, after which the serum is separated and if not clear it is centrifuged

A series of tubes is prepared each holding 1 0 cc of diluted buffer mixtures prepared from Baird & Tatlock s Universal Buffer Mixture varying from pH 8 4 to 5 0 in graduated steps of 0 04 Two drops of test serum are then added to each tube in the series The tubes are shaken and left standing for five minutes before readings are taken

The reactions are recorded as opalescent, faint cloudiness, cloudiness, and marked cloudiness Normal sera rarely show more than faint cloudiness at pH 7 0 and only an opalescence at 7 4 Strongly positive malarial sera will show cloudiness or marked cloudiness up to 8 0 or 8 4 or beyond, while weakly positive sera show cloudiness from 7 4

These results closely parallel those obtained from the melano-flocculation test

2 THE ICTERUS INDEX

A small but significant rise in the icterus index beyond the normal range of four to seven may lend support to a diagnosis of chronic or latent malaria

URINARY FINDINGS

Urobilinuria An increase in the urobilin content of the urine is a characteristic of acute malaria, but it may also be found in latent and chronic forms of the disease depending on the degree of haemolytic activity underlying the non acute forms

The tests designed to detect the urobilin increase include

1 *The Spectroscopic Test*

This test has to be carried out on a fresh specimen of urine which has been acidified with hydrochloric acid In the presence of an increase of urobilin a characteristic absorption band is seen at the junction of the blue and the green

Fresh normal urine fails to show any absorption bands

2 *The Schlesinger Test*

This constitutes a highly specific and reliable test for both urobilin and its chromogen urobilinogen Its sensitivity is somewhat impaired in the presence of albumin which absorbs small amounts of the pigment

The test consists in mixing and then filtering 10 cc of urine with the same volume of a well shaken suspension of 10% zinc acetate in absolute alcohol

Equal portions of the filtrate are then transferred to narrow test-tubes

A few drops of HCl are added to one test tube

Both tubes are then observed against a black background with lateral illumination

A greenish fluorescence indicates a positive urobilin reaction

A slight bluish tinge—the Tyndall phenomenon—should be ignored

Finally, by the addition of N/10 iodine to each tube any urobilinogen present is converted into urobilin

STERNAL PUNCTURE

Whilst the examination of the peripheral blood constitutes an integral part of the laboratory diagnosis of acute malaria, the examination of marrow smears obtained by sternal puncture may provide a valuable accessory procedure in the diagnosis of malaria in the chronic phase or modified by chemoprophylaxis Using a sternal puncture needle or a stout lumbar puncture needle, the sternum is punctured at the level of the second intercostal space at a point which lies just below the angle of Louis The skin over the centre of the sternum is anaesthetised The needle is inserted vertically and pressed firmly through the skin and subcutaneous tissue until the bony cortex of the sternum is encountered It is then forced into the bone by means of a to and fro rotatory movement or by gentle tapping with a small mastoid mallet, and in due course a sudden lessening of resistance indicates that the needle point has reached cancellous tissue The stilette is removed, and from 0 5 cc to 1 0 cc of marrow fluid aspirated

The marrow fluid may be oxalated, centrifuged and examined within 30 minutes, or preferably thick and thin smears are prepared at once, and after drying are stained by Giemsa's or Field s technique

Great care, patience and experience are necessary in the accurate interpretation of marrow smears on account of the multiplicity of artefacts encountered These include distorted platelets Howell Jolly bodies lying on a shadowy red corpuscle, basophilic red cells or portions of disintegrated myeloid cells The two features which assist in the identification of a plasmodium are malarial pigment and a containing red cell

In acute febrile malaria, marrow smears appear to have no particular advantage over peripheral blood as a means of diagnosis, but in chronic or latent malaria the chances of demonstrating plasmodia are undoubtedly greater in thick marrow smears provided the examiner is fully conversant with the difficulties of identification

CHAPTER SIX

DIFFERENTIAL DIAGNOSIS

ACUTE MALARIA

It has already been emphasised that acute malaria may simulate practically any acute febrile illness but in discussing the differential diagnosis it is proposed to deal with the common fevers of the Tropics only

A careful clinical history, the history of exposure to infection and the season of the year will provide clues to the possible malarial character of the fever, and in the case of Europeans the exclusion of malaria is a primary necessity in all acute febrile states But since the initial phases of so many fevers have so much in common, it may be exceedingly difficult, on clinical grounds alone, to establish a diagnosis hence the importance of blood smear examination in all febrile ills

The following conditions merit careful consideration in the differential diagnosis of acute malaria

ACUTE PNEUMONIC CONDITIONS

In an acute pneumonic attack the onset is abrupt with an initial rigor, but there is usually pain in the side of the chest together with a dry, restrained cough The breathing is rapid and a sticky blood stained sputum soon appears, while the physical signs of consolidation rapidly develop in the wake of an area of impaired air entry

ENTERIC FEVERS

While an attack of enteric fever may set in with an abrupt febrile reaction, there is more commonly a steady rise of temperature which will be unaffected by quinine therapy Headache, drowsiness and a gradual slowing of the pulse soon dominate the clinical picture, while tenderness in the right lower segment of the abdomen is common, with a certain amount of persistent gurgling when this area is palpated The abdominal reflex is absent

At this early stage of the illness, confirmation is obtained by means of blood culture

RELAPSING FEVER

It may be almost impossible to distinguish between relapsing fever and malaria at the onset of the first febrile paroxysm, but the flushed face and congested eyes, together with the photophobia, are more characteristic of relapsing fever than malaria However, the only certain means of establishing the diagnosis is by blood smear examinations during the pyrexial phase In relapsing fever spironemata will be found in the blood

THE TYPHUS FEVERS

In the tick or mite borne types, a primary eschar with regional lymphangitis and adenitis will indicate the probable nature of the fever, whilst the intense headache, diffuse body pains and later the characteristic rash will distinguish the attack from acute malaria

TRYPANOSOMIASIS

In acute trypanosomiasis a painless enlargement of the posterior cervical glands (Winterbottom's sign) is a common and valuable sign At the same time a circinate erythematous eruption or the appearance of localised oedemas of different parts of the body, more especially of the face, legs and feet, will constitute clinical evidence of the non-malarial character of the infection The diagnosis will rest finally with the demonstration of trypanosomes in the peripheral blood or in the juice from the enlarged cervical glands

YELLOW FEVER

While abortive and incomplete attacks add to the complexity of the yellow fever syndrome, the salient features of a typical attack include the rapid onset of severe prostration, early and increasing albuminuria with bradycardia and a gradually deepening icterus Violent fluctuations in temperature, drenching sweats and splenomegaly are not encountered in yellow fever

THE DENGUE—SAND-FLY FEVER GROUP

The initial clinical picture in this group of fevers may suggest an acute malarial attack, but the intense headache with pains in

the eyes, excruciating pains in the back and joints, and a bradycardia, constitute important clinical clues to the virus nature of the infection Further confirmation is obtained from the blood which shows a leucopenia with a relative lymphocytosis and an absence of malaria parasites

AMOEBIC HEPATITIS AND AMOEBIC ABSCESS

The existence of an amoebic hepatitis gives rise to pain and tenderness over the liver which is usually enlarged The spleen, on the other hand, is not palpable in uncomplicated amoebic hepatitis Blood *examinations reveal a neutrophilia*

In amoebic abscess of the liver a more exaggerated clinical picture is obtained, together with heavy sweats, rigors, loss of weight and emaciation There is thus an even closer resemblance to acute malarial attacks, but the presence of hepatic tenderness, the absence of splenomegaly, raising of the right leaf of the diaphragm, with possibly a right basal pleurisy, indicate the probable nature of the illness At the same time the blood shows a neutrophilia, and the recurrent rises of temperature fail to respond to quinine therapy

HEAT HYPERPYREXIA

The acute symptom-complex associated with heat hyperpyrexia is most likely to be confused with cerebral malaria, hence the only satisfactory differential procedure consists in careful examination of blood smears, both thick and thin In the absence of laboratory facilities the only logical procedure to adopt where the two conditions cannot be differentiated with certainty, is to administer 10 grains of quinine (well diluted) intravenously

THE DIFFERENTIAL DIAGNOSIS OF THE PERNICIOUS FORMS OF ACUTE MALIGNANT MALARIA

Since *Pl falciparum* infections are capable of giving rise to a massive infection of practically any organ or tissue, it follows that a wide range of grave febrile disorders will be encountered, more especially in the non immune European

The clinical grouping of these pernicious forms constitutes the basis of any scheme of differential diagnosis, so that a detailed list *of the acute febrile conditions with which* malignant malaria may be confused becomes necessary

It is, therefore, apparent that in the presence of any fulminating fever in the Tropics, the exclusion of acute malignant malaria should be regarded as an elementary step in the investigation of the primary cause

This precaution is especially necessary in the presence of any acute fever in which the presenting features indicate involvement of the central nervous system, abdomen or cardio-vascular system, nor must it be forgotten that malignant malaria may assume an afebrile algid form in which a state of grave collapse dominates the clinical picture So long as the practising physician and surgeon keeps malaria well in mind at all times, dangerous errors of diagnosis will be avoided when dealing with apparent cases of acute meningitis, otitis media, heat hyperpyrexia, acute cholecystitis, acute pancreatitis, perforated peptic ulcer, haematemesis, acute bacillary dysentery and coronary thrombosis

It is clearly necessary to observe the greatest precision in the diagnosis of each and every tropical fever and also in every case of collapse for which no obvious cause can be found, if lives are to be saved through the prompt and efficient use of the anti malarial drugs

DIFFERENTIAL DIAGNOSIS OF CHRONIC MALARIA

In Africa the main tropical disorders with which chronic malaria may be confused are

Bilharziasis,
Ankylostomiasis
Kala azar

At the same time any chronic debilitating disease accompanied by splenomegaly may simulate chronic malaria, especially when the syndrome evolves in relation to a malarial background For this reason it may be necessary to pass in review a varied range of dis orders including leukaemia, lymphadenoma, splenic anaemia, acholuric jaundice, erythraemia, amyloid disease, syphilis, tuber-

BILHARZIASIS

In the chronic phase of both urinary and intestinal bilharziasis, a rise of temperature occurs at irregular intervals, while splenomegaly and hepatomegaly can usually be demonstrated

These findings, together with loss of weight and a state of general debility, may be ascribed to chronic malaria, but in bilharziasis the characteristic ova appear in the stool and urine samples (although prolonged search of repeated specimens may be necessary), and characteristic bilharzial lesions will be demonstrable on cystoscopic examination of the bladder or on sigmoidoscopic examination of the lower bowel

The blood findings in chronic bilharziasis generally fail to reveal any significant degree of eosinophilia, but a diagnostic titre will always be obtained with Fairley's complement fixation test

ANKYLOSTOMIASIS

In this disorder, loss of weight, lassitude and anaemia with icteric tinging of the skin may suggest chronic malaria, but the absence of splenomegaly suggests a non malarial background, and the presence of hookworm ova in the stool will provide the diagnosis, although it may not necessarily constitute the full explanation of the syndrome in view of the frequency with which polyparasitism is encountered in the tropics

KALA AZAR

This condition bears a very close resemblance to chronic malaria by reason of the intermittent pyrexia, anaemia, splenomegaly and cachexia, all of which the two diseases have in common

Consequently the diagnosis rests ultimately on the demonstration of Leishman Donovan bodies in the juice aspirated from the liver or spleen or cultured from the peripheral blood Kala azar will fail to respond to quinine therapy

Finally it may be stressed that when dealing with any chronic syndrome for which no adequate explanation can be found, it is always worth while to investigate the patient carefully for evidence of chronic malaria In this way intractable headaches a migrainous syndrome, neuritis, especially a mono neuritis, tachycardias and even certain psychoses may be found to have a malarial background, the elimination of which clears up the complaint

CHAPTER SEVEN

PROGNOSIS AND TREATMENT

PROGNOSIS

The prognosis in acute malaria is determined by the species of the infecting parasite, rapidity of diagnosis and efficiency of treatment, but the outcome of a given attack will also be influenced by such factors as the age, race and state of health of the individual

Acute malaria is always a dangerous disease in infants and young children, whether European or African This is especially true of childhood attacks of acute malignant malaria, which is prone to merge suddenly into a cerebral attack

On the other hand the mortality rate from malaria amongst the adult African population living in an endemic area is entirely neglig ible *But in the presence of debilitating conditions such as ankylo*stomiasis, bilharziasis, avitaminosis, syphilis, tuberculosis and so on, acute malaria becomes a more serious disease with a correspond ingly higher death rate in all population groups

With these various conditions in mind it may be claimed that acute benign malaria (as the name implies) has in the main a good prog nosis, even though exceptions to the rule can be quoted On the other hand the benign forms show a high relapse rate

In acute malignant malaria the danger lies in the onset of pernicious forms such as algid or cerebral malaria which render the outlook grave in the extreme Finally, in the presence of repeated infections with *Pl falciparum* there is an inherent risk of blackwater fever and with it an entirely new set of adverse prognostic factors

With chronic malaria the danger to life rests not so much with the malarial infection as such, but with a state of enhanced suscept ibility to intercurrent infections such as bronchopneumonia and bacillary dysentery which tend to terminate fatally

But both the anaemia and cachexia which characterise chronic malaria in Europeans will usually respond well to routine treatment

with iron and vitamins once the plasmodial infection has been eliminated

TREATMENT

GENERAL MANAGEMENT

During an acute attack of malaria *the patient should be put to* bed and recumbency continued until the temperature has been normal (or more likely subnormal) for a matter of three or four days A mosquito net should always be used from just before sundown until the following morning

For the immediate relief of symptoms a tepid (80° F) sponge-down of the entire body will have a soothing and refreshing effect and at the same time a tonic effect on the vasomotor system Sponging will also be necessary at the termination of the sweating stage [illegible]

[illegible] it there until specific drug therapy becomes effective

For the headache, myalgic pains and general malaise a simple diaphoretic mixture or a combination of five grains of aspirin and five grains of Dover's powder will usually give adequate relief and may be repeated after an interval of four to six hours

Restlessness at night and inability to sleep can usually be counteracted by a simple barbiturate, a bromide mixture or even 15 grains of Dover's powder Very occasionally severe pain in the splenic region may necessitate a gr *1/6* or gr *1/4 of morphine to ensure a* good night's rest at the onset of the attack

Nausea and vomiting will usually respond to vigorous antimalarial therapy, but where this has been delayed or has been ineffective an intravenous drip saline becomes necessary to offset dangerous dehydration

[illegible]

acute attack of malaria

Since the febrile phase in malaria is of short duration the diet should be restricted to fluids initially Each feed should consist of 5 to 6 oz of fluid administered every two hours Fruit juices are well

tolerated when sweetened with glucose, and have a greatly enhanced food value Other fluids include citrated milk (two grains of sodium citrate to the oz.), barley water flavoured with orange or lemon juice, weak tea or clear soup Jellies and custards may be included in the dietary if desired Barley sugar should be kept by the bedside and taken at any time, while a free intake of plain water should be encouraged

SPECIFIC DRUG THERAPY

THE PLASMOCIDAL DRUGS

1 QUININE

Cinchona bark, from which quinine is obtained, reached Europe from Peru in 1640, whence it was brought by the wife of the Spanish Viceroy of Peru, the Countess Cinchon It is popularly held though not necessarily historically correct, that the Countess had been rapidly cured of a fever by means of the powdered bark of what came to be known as the Cinchona tree

The crude bark continued in use in Europe until early in the 19th century when Gomez of Portugal isolated a substance he termed cinchonine (1810 *vel* 1815) Ten years later cinchonine was shown by the French chemists Pelletier and Caventou to be made up of two alkaloids which they named quinine and cinchonine Upwards of a score of alkaloids have been isolated from cinchona bark since then, and although some of them, e g, quinidine, have been shown to be actively plasmocidal they have all been set aside in favour of the crystallizable alkaloid quinine by reason of their greater toxicity or (e g, cinchonidine) lack of therapeutic efficiency

The cinchona alkaloids are derived from the bark of the Cinchona tree, originally indigenous to Western South America, but subsequently brought to Ceylon and Java which became the major source of the world's quinine supplies Of the various species of Cinchona, *C succirubra* and *C calisaya* are extensively cultivated in India where they constitute the main sources of quinine, even though the yield is small (1 5 to 3 5%) In Java, on the other hand, the dominant species is the more delicate *C ledgeriana* with a quinine yield of 3 to 8% or more This species is commonly grafted on to *C succirubra*, thereby ensuring a hardy plant and a high yield of alkaloid

Since the base (quinine alkaloid) is insoluble, *quinine is usually* administered in the form of a soluble salt The salts most commonly employed include (1) the sulphate and the hydrochloride, both of which have one molecule equivalent of acid and give an almost neutral solution but are not very soluble, and (2) the bisulphate and the bihydrochloride with two acid equivalents, a high solubility with a resultant strongly acid solution due to the liberation of free sulphuric or hydrochloric acid by hydrolysis, and (3) the dihydrobromide and the ethyl carbonate of quinine

For economic reasons extracts containing the combined alkaloids of cinchona bark have been employed at different times They have been prepared from barks with a low quinine yield, e g , *C succirubra* Thus quinetum was prepared from *C succirubra* in India, and later "cinchona febrifuge" was evolved from the residual alkaloids after extraction of quinine Since the actual quinine content of these total alkaloid preparations varied widely, the League of Nations Malaria Commission advocated the use of a standardised product termed "Totaquin" in those countries manufacturing "cinchona febrifuge" It was laid down that Totaquin must contain at least 70% crystallizable alkaloids, of which at least one fifth must be quinine Amorphous alkaloids must not exceed 20%, while mineral substances and water were limited to 5% It is obvious, however, that these crude preparations contain a high percentage of inert material, thereby impairing the therapeutic efficiency of the active components

THERAPEUTIC ACTION

It is probable that the therapeutic value of quinine in malaria is due to its plasmocidal property rather than to any indirect action it may have on the immunity mechanism of the body

This view receives support from the rapidity with which quinine *acts in acute malaria, especially when administered intramuscularly* or intravenously Again, both under experimental conditions in the ape and in naturally occurring infections in man, the plasmocidal action of quinine is in no way impaired by the absence of a spleen, which constitutes an integral part of the immunity mechanism in malarial infections

Unlike undifferentiated protoplasm, the malaria parasite shows

important variations in its vulnerability to quinine The sexual forms are unaffected by ordinary therapeutic doses of the drug while the available evidence suggests that the exo-erythrocytic forms of the parasite are also immune Hence the therapeutic value of quinine in malaria lies in its powerful action on the merozoites as they circulate as free bodies in the plasma, and on the developing schizonts within the red corpuscles

Quinine is rapidly absorbed and can be demonstrated in the urine within 15 minutes of being taken by mouth The excretion rate is a variable quantity, but about a third of that absorbed appears in the urine, with traces in the faeces, saliva and milk Just under two-thirds is destroyed in the tissues About two-thirds of the quinine absorbed is excreted in the first 12 hours, and most of the remainder within the next 24 hours The amount and rate of excretion is roughly the same whether the quinine is given orally, intramuscularly or intravenously The rapidity with which quinine is excreted or destroyed in the tissues necessitates using large doses fairly frequently if an efficient concentration of the drug is to be maintained in the blood stream

Methods of Administration Quinine salts may be administered orally, intramuscularly or intravenously

ORAL ADMINISTRATION

Quinine is given by the mouth whenever the clinical state permits Although administered either in solution or in tablet form it is always more efficacious and therefore preferable to prescribe quinine in a mixture in the treatment of malaria The sulphate of quinine is entirely suitable for the purpose, and there is no advantage in prescribing either the bihydrochloride or bisulphate on the ground of their greater solubility The sulphate is readily brought into solu [illegible]

[illegible]

mixture of quinine

Quinine sulphate	10 grains
Dilute sulphuric acid B P	10 minims
Syrup of ginger	*q.s*
Cinnamon water, to half an ounce	

or

Quinine sulphate	10 grains
Citric acid	30 grains
Syrup of ginger	*q.s*
Cinnamon water, to half an ounce	

Given as a mixture the quinine is rapidly and completely absorbed with speedy control of the malarial paroxysms (dilute hydrobromic acid is sometimes added to the formulae (1 minim to 1 grain) with the object of reducing tinnitus), whereas tablets may fail to dis integrate and may traverse the intestinal tract unchanged When tablets have been stored for any length of time they must be examined periodically to ascertain their capacity for disintegration in the gastro intestine To this end a tablet should be placed in a glass of lukewarm water and should begin to disintegrate within a few minutes Complete solution is not necessary but failure to disintegrate at all after an hour or so means that the tablet will almost certainly pass unabsorbed through the intestine

INTRAMUSCULAR ADMINISTRATION

In the treatment of acute malaria, especially acute malignant malaria, it is frequently necessary to administer quinine by the intramuscular route in order to obtain speedy and effective control of the infection Neglect of this procedure may seriously jeopardise the prognosis

The main indications for the employment of quinine intra musculariy are as follows —

1 Persistent and violent vomiting
2 A heavy infection of the peripheral blood in *Pl falciparum* infections,
3 The presence of pernicious forms of acute malignant malaria or a clinically severe attack whatever the species of the infecting plasmodium,
4 Wherever there is reason to suspect ineffective absorption of quinine administered orally,
5 Whenever an attack of malaria complicates the puerperium the post operative state or any illness such as pneumonia which *has already given rise to a state of debility*

It should be emphasised, however, that it is only necessary to utilise the intramuscular route as a means of bringing the malarial

attack under control so that in the majority of cases it should never be necessary to administer more than two or at most three intramuscular injections, after which treatment may be continued and completed by means of quinine given orally

The dose given intramuscularly is usually 10 grains of quinine bihydrochloride dissolved in 1 0 cc to 2 0 cc of sterile water, and it should be remembered that a certain amount of pain is experienced locally during the injection but the pain does not radiate and does not persist The site usually selected for the injection is the upper outer quadrant of the buttock in order to avoid injury to the sciatic nerve fibres Once the injection has been given the site is gently massaged to disperse the solution and so avoid extensive muscle necrosis

It is obvious, therefore, that the intramuscular administration of quinine is not without danger Some necrosis of muscle tissue is always caused by quinine and should infection of the necrosed tissue set in, abscess formation with extensive sloughing and a prolonged spell of invalidism will result Gas gangrene, tetanus and general septicaemia have also been listed as complications of intramuscular quinine, but the incidence of such major disasters must be extremely low A more common complication is the gradual formation of a small indurated nodule at the injection site which may last for years and may give rise to a certain amount of local discomfort or even pain from time to time It has sometimes been found necessary to excise the nodule in later years

Finally, the injection of quinine into or near the sciatic nerve has been responsible for paralysis of the ham strings and all the muscles below the knee with foot drop and inability to flex the knee

But these potential dangers fade into insignificance when a maximum of care is exercised in the maintenance of a strictly sterile technique and in the selection of the site for injection

Thus intramuscular quinine therapy constitutes an important therapeutic weapon in the treatment of acute malaria

INTRAVENOUS ADMINISTRATION

Intravenous quinine therapy is usually reserved for the pernicious varieties of acute malignant malaria where the urgency of the clinical features demands rapid and immediate control of the infection.

This is especially the case in cerebral malaria in which the transition to a state of fatal coma may occur with alarming speed

It cannot be said, however, that intravenous quinine is desirable in all the pernicious forms of malignant malaria In abdominal and in algid malaria, for example, the degree of vasomotor collapse is such that any further depression caused by intravenous quinine therapy is more than likely to bring about fatal syncope

In such cases (as will be seen later) it is more profitable to give an intravenous glucose saline to which 10 grains of quinine have been added while at the same time 10 grains have been given intra muscularly

When administered intravenously the bihydrochloride of quinine is employed in a dose (for an adult) of 10 grains dissolved in 20 cc of sterile water or 5% glucose saline The injection is given very slowly to obviate an abrupt fall in blood pressure

When properly administered the injection is painless and in favour able circumstances a satisfactory clinical response is obtained But it must never be forgotten that a rapid flooding of the circulation with quinine is capable of precipitating a fatal collapse There is too the added danger that an over rapid destruction of parasites may induce a modified Herxheimer reaction

However, the dangers inherent in the intravenous administration of quinine are largely offset by a careful assessment of the clinical circumstances combined with meticulous attention to the details of technique Once it is obvious that an attack is coming under control oral therapy should be started

TOXIC EFFECTS OF QUININE

The administration of quinine in therapeutic doses gives rise to a mild symptom-complex known as cinchonism with deafness and buzzing or ringing in the ears as the main presenting features These symptoms usually appear during the early stages of quinine medica tion, but are temporary in character in that they disappear with the cessation of treatment, and may be said to constitute a useful clinical index of quinine absorption

Other side effects of a more troublesome nature include nausea, a feeling of dizziness, tremor or palpitation, while the precipitate

administration of quinine intravenously may result in an abrupt fall in the blood pressure with the risk of fatal collapse

In the ordinary way, however, the features of cinchonism do not *necessitate suspending quinine therapy* Over and above these characteristic side effects some patients exhibit a hyper sensitivity to quinine which may express itself in a variety of ways

1 *Cutaneous eruptions* These vary from a diffuse erythema or scarlatiniform eruption to an urticaria which may vesiculate In some cases a true allergic eczema develops with extensive oedema of the dermis In such cases the clinical picture bears a close resemblance to exfoliative dermatitis

2 *Localised oedemas* may develop in relation to the mucous membranes of the nasopharynx, oral cavity or the bronchial and alimentary tracts, causing acute syndromes characterised by dyspnoea with pulmonary oedema or violent attacks of vomiting or purging accompanied by cardio-vascular collapse

3 *Purpuric haemorrhages* may develop in relation to the skin or mucous membranes, causing a purpuric eruption which may attain the severity of a purpura haemorrhagica or may be characterised by intractable haemorrhage from the nose, mouth, bowel or urinary tract

4 *Visual disturbances* Retinal damage leading to amaurosis may be caused by quinine, but is a relatively rare complication The lesions in the retina develop abruptly, are bilateral and are characterised by rapid shrinkage of the visual fields, culminating in complete blindness This complication is liable to be followed by optic atrophy

5 *Permanent deafness* This is a rare but possible complication when massive doses of quinine are being given over an unnecessarily long period of time

ANTIDOTES TO CINCHONISM

It is claimed that the toxic effects of quinine can be lessened by means of peptone orally in 7½ grain doses given 30 minutes before each dose of quinine Potassium bromide, caffeine and adrenalin have also been recommended

It is now possible, however, to make use of alternative plasmocidal drugs in the presence of quinine intoxication or allergy

2 MEPACRINE (ATEBRIN)

Mepacrine is a synthetic acridine derivative with plasmocidal properties It was produced in 1930 by Kikuth and his collaborators, Mietzsch and Mauss, at the I G Farbenindustrie, Elberfeld, where it was found to exert a powerful plasmocidal effect on the parasites of bird malaria Shortly afterwards its therapeutic efficacy in all types of human malaria was established and confirmed by workers in all parts of the Tropics

The drug is a bright yellow crystalline powder with a bitter taste and sparingly soluble in water, giving a neutral fluorescent solution It is available for oral administration in tablet form, each tablet containing 0 1 G (1½ grains) of the drug A soluble form of the drug known as mepacrine methane-sulphonate (B P) (Atebrin musonate (Bayer), Quinacrine soluble (Pharmaceutical specialties)) is suitable for parenteral therapy, and may be given either intramuscularly or, in very urgent cases, intravenously

Mepacrine methane sulphonate is a yellow crystalline powder soluble 1 in 3 in water It is put up in ampoules containing 0 375 G of the drug and is equivalent to 0 3 G of mepacrine hydrochloride Before administration the powder is dissolved in 5 0 cc of sterile distilled water and injected immediately

Mepacrine is rapidly absorbed, whether given orally or intramuscularly, and is excreted very slowly, unchanged in the urine It appears in the urine about the second day, and persists for two or three weeks after cessation of treatment It is believed that a certain amount of the drug is excreted in the bile, but is subsequently reabsorbed, thereby prolonging its therapeutic action

THERAPEUTIC ACTION

Mepacrine exerts a powerful plasmocidal action on the asexual forms of all the malaria parasites It has been shown microscopically that vacuolation and fragmentation of the plasmodial cytoplasm occurs, followed by disintegration of the chromatin and complete disappearance of the pigment

While it is probable that these changes represent a direct parasiticidal effect, it does not entirely preclude the possibility of the enhanced action of indirect biological factors

Mepacrine, however, has little or no value as a gametocide, especially in respect of the crescent forms of *Pl falciparum* Nor does it appear to have any destructive influence on the exo-erythrocytic forms of *Pl vivax* as revealed by the relapse rate after treatment and the development of an overt attack of benign malaria within a few weeks of discontinuing "suppressive" mepacrine prophylaxis

Methods of Administration Mepacrine may be given (1) orally in the form of mepacrine hydrochloride, or (2) intramuscularly or intravenously as mepacrine methane sulphonate

ORAL ADMINISTRATION

When administered orally mepacrine hydrochloride is given in tablet form, each tablet containing 0 1 G (1½ grains) The dose should be taken with plenty of fluid and immediately after food if meals are being taken In the case of adults and older children the tablet should always be swallowed whole in view of its intensely bitter taste, but with very young children it may be necessary to crush the tablet and give it in milk or concealed in a spoonful of jelly The average daily dose for an adult is 0 3 G, but in the case of very heavy patients weighing 12 to 13 stones or over, the daily dose should be increased to 0 4 G

In the case of children the following daily dosage scheme is recommended

Up to one year	0 05 G (i e, half a tablet)
One to four years	*0·1 G*
Five to eight years	0·2 G
Over eight years	0·3 G

PARENTERAL ADMINISTRATION

The circumstances which justify and necessitate using quinine either intramuscularly or intravenously in controlling an acute malarial attack will also necessitate parenteral mepacrine therapy when that drug is being used solely in the treatment of an attack

Thus intramuscular injections of mepacrine are given in the presence of persistent vomiting, pernicious symptoms, a heavy plasmodial infection of the peripheral blood and so on In the case of adults 0·36 G of mepacrine methane-sulphonate dissolved in 5 cc

of sterile distilled water is injected into the gluteal region and the dose repeated in 12 hours If the clinical state permits the treatment course is then completed orally over a period of five days

The intramuscular dosage scheme for children is as follows

Up to four years	0 1 G
From five to eight years	0 2 G
Over eight years	0 3 G

The indications for intravenous mepacrine therapy are the same as those listed for intravenous quinine, but there is a fairly general (though not necessarily logical) tendency to use quinine intravenously rather than mepacrine when faced with urgent and dangerous pernicious symptoms

While the intravenous dose of mepacrine methane sulphonate is given as 0 3 G for the adult, it is probably safer to use 0 2 G and give 0 15 G intramuscularly at the same time As in all forms of intravenous therapy the injection must be given slowly and may be combined with 0 5 cc of 1 in 1,000 solution of adrenalin Although a temporary fall in blood pressure has been noted both in man and in animals during the intravenous administration of mepacrine, serious collapse has seldom been observed and so far as can be ascertained clinically, mepacrine does not affect the myocardium adversely

TOXIC AND SIDE EFFECTS OF MEPACRINE

1 *Gastro-intestinal Upsets* When taken orally mepacrine may give rise to a certain amount of epigastric discomfort with nausea and possibly vomiting The vomiting may be persistent enough to necessitate abandoning oral in favour of parenteral therapy

Abdominal cramps are sometimes experienced, especially when the bowel is constipated They usually disappear after adequate evacuation of the bowel

Severe abdominal pain was a frequent occurrence when it was customary to administer mepacrine and plasmoquine simultaneously

In a few cases mild diarrhoea persists throughout the course of mepacrine therapy

2 *Headaches and Giddiness* In a few instances headache and giddiness constitute unpleasant features of a treatment course

3 *Psychological Disturbances* These disturbances, which fortunately are not common amongst the European races range from a state of mild cerebral excitement with insomnia or lively dreams to a true toxic psychosis which usually assumes the characteristics of an acute confusional insanity of the maniacal type

The patient is restless and sleepless talks incessantly in a rambling incoherent manner exhibiting a wild flight of ideas and tends to shout and scream and may even become violent when restrained in any way

Fortunately, the psychosis is usually of a temporary nature, but it may be many months before mental stability is regained Indeed temporary certification is not infrequently necessary

It appears that certain Far Eastern racial groups are especially prone to mepacrine psychosis but there can be no question of the European races enjoying complete immunity from this alarming toxic effect

Apart from temporary mental derangement transient epileptiform convulsions have also been described in Tamils

4 *Yellow Staining of the Skin* Yellow colouration of the skin is a frequent accompaniment of mepacrine administration whether therapeutic or prophylactic The staining appears during or soon after a treatment course and is due to deposition of the acridine pigment in the dermis It persists for three or four weeks or more

The staining is usually most pronounced over the front of the chest and abdomen but is not associated either with irritation or photosensitivity Staining of the sclera is also found

3 PAMAQUIN

Pamaquin is a synthetic quinoline compound prepared in 1924 by Schuleman Schonhofer and Wingler and originally known as plasmoquine Its plasmocidal efficacy in avian malaria was demonstrated by Rohl in 1926 and soon afterwards the drug was introduced into the treatment of human malaria

Pamaquin is a pale yellow granular powder insoluble in water but readily soluble in alcohol

THERAPEUTIC ACTION

It destroys the asexual forms of *Pl vivax* and *Pl malariae* but is a poor schizonticide in *Pl falciparum* infections. On the other hand

pamaquin is an active gametocide in all types of infection with a highly selective action on the crescent forms of *Pl falciparum* It can be shown microscopically that in the presence of pamaquin the crescents become irregular in outline and then rapidly disintegrate, leaving a deposit of granular pigment

While the drug may be employed in the treatment of an attack of acute benign malaria, it is valueless in acute malignant malaria In the current therapeutics of malaria, therefore, pamaquin is employed in a supplementary sense after the acute attack has been controlled by means of quinine or mepacrine Its main value lies in its gametocidal properties which render the convalescent patient non-infective to mosquitoes, and in its capacity for reducing the relapse rate in acute benign malaria

METHODS OF ADMINISTRATION

While pamaquin may be administered parenterally, the oral route is the only one that need be considered Only in very exceptional circumstances will the intramuscular route be necessary, while intravenous therapy is both useless and dangerous

The drug is given in the form of small tablets of 0 01 G and is best given immediately after a meal When given concurrently with mepacrine the toxic effects of both drugs are sharply enhanced, and attacks of severe abdominal colic are common

When given as a follow up to quinine or mepacrine therapy, the usual dosage scheme for pamaquin is 0 01 G thrice daily for five days

TOXIC EFFECTS

Pamaquin therapy is complicated by the narrow margin that exists between the therapeutic and the toxic dose, hence when first used in the treatment of malaria toxic symptoms were of frequent occurrence on account of the heavier doses employed at that time

On the other hand toxic effects may be induced by extremely small doses of the drug, but usually when treatment has extended over a period of six to nine days

The chief toxic effects that may arise during pamaquin therapy are as follows

1 *Abdominal pain* in the form of dull persistent ache in the

epigastrium The underlying cause is probably a state of pylorospasm, but whatever the cause, the pain is rendered very acute by administering mepacrine simultaneously (a procedure no longer followed)

2 *Cyanosis* Cyanosis, especially of the lips, ears and finger nails, *tends to occur in susceptible patients or whenever heavy doses are* being employed

The phenomenon is conditioned by the intracorpuscular formation of methaemoglobin, thereby impeding free oxygenation of the red cells, so that when the attack is at its height the affected areas may look almost black Dyspnoea is not a feature of the attack but a state of weakness together with a severe headache dominates the clinical picture

3 *Cardiac Arrhythmia* Temporary disturbances in the cardiac rhythm may arise in the course of pamaquin treatment

4 *Haemolytic Anaemia with Methaemoglobinuria* A severe form of anaemia has been described in highly susceptible individuals, and is usually accompanied by methaemoglobinuria. In such circumstances the condition is liable to be confused with blackwater fever Cases which *terminate fatally show an acute yellow atrophy of the* liver

4 PALUDRINE*

The discovery of pamaquin and mepacrine was followed by an extensive study of the quinoline and acridine nuclei but no significant advances have been made on the original discoveries More recently, therefore, attention was directed to other hetero-cyclic ring systems and for a variety of reasons the pyrimidine nucleus was chosen as a new basis in the search for a potent and easily prepared plasmocidal drug. The chemistry of its ring structure had already been well studied in relation to sulphapyrimidine, and it had the added advantage that its molecular structure lent itself to the introduction of chemical groupings of known anti malarial properties Closely linked with these chemical studies was the problem of a biological test of sufficient sensitivity to detect traces of anti malarial activity in any given compound, and after careful comparative study it was decided that *Pl gallinaceum* infection in chicks provided a satisfactory means of detecting these important lesser degrees of

*See also addendum on page 101

plasmocidal activity By means of this biological test a moderate degree of plasmocidal activity was detected when a dialkylaminoalkylamino side-change was added to the pyrimidine nucleus (Compound 2666), but when tested against human malaria, the drug was clinically unsuccessful

This initial discovery was *followed up by a close study of the* tautomers of the 2666 molecule, and the conclusion was reached that a central ring system is not essential to anti malarial activity, but that any system presenting the necessary alternation of nitrogen and carbon atoms with the appropriate double bonds could have plasmocidal properties

These simplified conditions are fulfilled by the biguanides, and after a series of brilliant chemotherapeutic studies by a group of British chemists a compound now known as Paludrine Hydrochloride was evolved, and probably represents the highest level of plasmocidal activity attainable with the biguanide grouping

THERAPEUTIC ACTION

The meticulously careful war time studies carried out at the Liverpool School of Tropical Medicine and by Fairley and his team at Cairns in Australia, served to establish the pre-eminence of paludrine in *the therapeutics of human malaria*

The initial studies in avian malaria had already revealed the interesting fact that the powerful plasmocidal action of the drug is exerted on the schizonts and on the exo-erythrocytic forms of the parasite Consequently paludrine was found to exert a causal prophylactic as well as a therapeutic action against *Pl gallinaceum* (in chicks), *Pl cathemerium* (in canaries), *Pl lophurae* (in chicks) and *Pl relictum* (in canaries)

Until the discovery of paludrine, pamaquin had been the only drug capable of destroying pre-erythrocytic forms of the malaria parasite, but the toxicity of the drug precluded it from general use in the chemoprophylaxis of malaria

When the study of the therapeutic properties of paludrine was extended to human malaria, it soon became apparent that the action of the drug was not restricted to the trophozoites alone, but involved the hypothetical pre-erythrocytic forms of the parasite At the same *time experimental evidence derived from human volunteers showed*

that paludrine is probably incapable of destroying sporozoites at the time of their inoculation into man so that it becomes necessary to conclude that its prophylactic property is based on its lethal action on the pre-erythrocytic forms of the plasmodium This action is probably the result of arrested nuclear function

In the case of *Pl falciparum* infections the systematic administration of paludrine will in due course effect the complete destruction of all the exo-erythrocytic forms so that schizonts fail to appear in the blood and in this way the infection is completely eliminated Thus in *Pl falciparum* infections paludrine is a true and complete causal prophylactic

In *Pl vivax* infections on the other hand, the destruction of the exo-erythrocytic forms of the parasite is evidently incomplete, and in consequence, withdrawal of paludrine is followed in due course by the appearance of schizonts in the red cells and the onset of overt malaria as a sequel to uninhibited schizogony In the case of *Pl vivax* infections paludrine must therefore be classed as a partial causal prophylactic

When administered therapeutically in overt malaria, paludrine acts on the young schizonts at the stage of chromatin dispersal and just before division of the cytoplasm takes place The schizont becomes swollen and vacuolated and the chromatin gradually disintegrates In this way merozoites fail to develop and febrile paroxysms are prevented

The drug has also an important action both on the process of gametogony and on the gametocytes themselves

When given at the very onset of a malarial attack the widespread destruction of trophozoites leads in turn to a relative failure in gametocyte production in view of the fact that gametocytes evolve in the wake of the primary schizogony cycles

While morphologically no significant changes can be seen in gametocytes exposed to the action of paludrine, far reaching biological effects have been clearly established.

When taken up by the appropriate mosquito the gametocytes of both *Pl vivax* and *Pl falciparum* undergo exflagellation and fertilization with the formation of a zygote which may develop as far as the oöcyst stage but wherever traces of paludrine appear in the blood-feed the sporogony cycle fails at this point with complete sterliza-

tion of the gut This phenomena as described persists until all traces of paludrine have been eliminated from the human host In the event of the blood stream containing a high concentration of paludrine when the mosquito takes up its feed of gametocyte-containing blood, the sporogony cycle is virtually eliminated in that even fusion of the germinal elements fails to occur

But in view of the absence of any direct action by paludrine on malarial gametocytes it is important to realise that once the drug has been completely eliminated the gametocytes may regain their infectivity thereby restoring the "carrier state"

However, it is obvious that the influence of paludrine on the biology of the gametocyte constitutes a factor of major importance in controlling the spread of malaria

METHOD OF ADMINISTRATION

Paludrine hydrochloride is given daily in tablet form, each tablet containing 100 mgms (0 1 G)

In acute malignant malaria due to *Pl falciparum* radical cures have been effected by administering 100 mgms three times a day for 10 days or 100 mgms twice a day for 14 days In acute benign malaria due either to *Pl vivax*, *Pl ovale* or *Pl malariae* the optimum standard course has not yet been determined While benign attacks may be cut short and temperatures reduced to normal values by a single dose of 100 mgm of paludrine radical cure cannot be guaranteed, hence a maintenance dose of 100 mgm each week will avert relapses indefinitely It has been suggested that 300 mgm of paludrine daily for 21 days would constitute an overall course for acute benign malaria followed by 100 mgms twice a week for at least six months

From the view-point of chemoprophylaxis in malaria paludrine represents a therapeutic achievement of the first magnitude

As mentioned above it constitutes a true causal prophylactic in infections with *Pl falciparum*, but in view of its failure to effect complete elimination of all pre-erythrocytic forms in *Pl vivax* infections it can only be classed as a partial causal prophylactic

In the causal prophylaxis of *Pl falciparum* infections a dosage of 100 mgms of paludrine hydrochloride is recommended twice a week (every Wednesday and Sunday) throughout the malaria "season".

THE TOXICITY OF PALUDRINE

In discussing the toxicity of paludrine it should be appreciated that the toxic effects so far observed have appeared in relation to doses far in excess of those normally employed in the chemotherapeutics of malaria There is clearly a wide margin of safety between the therapeutic and potentially toxic dose, but it is possible that cases of idiosyncrasy or allergy to the drug will eventually emerge as the drug is used on an ever increasing scale

When for experimental purposes, paludrine was being tested in extremely high doses in human volunteers, the following toxic effects were observed in some cases

(1) Vomiting occurred when cases of overt malaria received 1,000 mgms of paludrine daily, but in only one case (in which oesophageal spasm occurred) was it found necessary to suspend paludrine therapy altogether Whenever vomiting has occurred a temporary withdrawal of the drug for 24 to 48 hours or a reduction in the dosage has served to allay the vomiting

In two instances the administration of paludrine in a single dose of 1,000 mgms gave rise to abdominal pain, vomiting and some diarrhoea These symptoms persisted for about 12 hours.

(2) In the presence of a continued high dosage (e g, 1,000 mgms daily for 14 days) evidence of irritation of the renal tract appears in the form of haematuria accompanied by sheets of epithelial cells, probably derived from the lower reaches of the renal tract, together with a few hyaline and granular casts, So far there is no evidence that paludrine gives rise to an acute parenchymatous nephritis

(3) The only observed effect of plaudrine on the haemopoietic tissue consists in the transient appearance of myelocytes in the peripheral blood following the administration of heavy doses This phenomenon is only observed in relation to overt malaria and bears a direct relationship to the dosage employed It is thought to be due to the direct action of paludrine on the bone marrow No tendency to agranulocytosis has so far been observed

OTHER PLASMOCIDAL DRUGS

It is not proposed to deal with these drugs in any detail, as have little or no practical value in the current therapeutics of ma

METHYLENE BLUE

This drug was employed in the treatment of malaria by E and Guttman as far back as 1891 It has little or no action on tions with *Pl vivax* or *Pl falciparum*, but is definitely plasm towards *Pl malariae*, destroying both the schizonts and the g tocytes The drug is given orally in capsules containing either 3 grains with a total daily dose of 15 grains The urine and the are stained blue, and in some cases strangury occurs as a com tion

ARSENICALS

The drugs included in this group are for the most part useful malarial tonics, although in some cases a direct plasmocidal a can be demonstrated

NOVARSENOBILLON (N A B)

Whittingham claims that N A B not only destroys plasmodia, at the same time exhibits an adrenalin like action whereby the p site content of the peripheral circulation is increased, and in circumstances both quinine and mepacrine act with greater effici However, it will usually be found that relapses occur wherever N is employed as the sole plasmocidal agent, so that it is wiser to re the drug as a valuable post malarial tonic For this purpose a us dosage scheme consists in 0 3 G to 0 45 G given intravenous weekly intervals for three injections

MAPHARSEN

It is stated that a single intravenous injection of mapharsen terminate an attack of acute benign malaria (*Pl vivax*) in 90% cases The dosage employed varies from 0 04 to 0 06 G accor to body weight So far, however, mapharsen therapy appears have been restricted to cases of therapeutic malaria

STOVARSOL

Here again the preparation constitutes an effective post malarial tonic, but when combined with quinine as quiniostovarsol acquires moderate plasmocidal properties

THE SULPHONAMIDES

Recent experimental work on the therapeutic range of the sulphonamides has revealed an activity against *Pl gallinaceum* in chicks, *Pl lophurae* in ducks and *Pl knowlesi* in monkeys They are inactive against *Pl inui* in monkeys and *Pl relictum* in canaries and pigeons

In regard to human malaria they show a variable range of plasmocidal activity Recent work has shown that preparations such as sulphadiazine sulphamerazine and sulphamethazine are all capable of destroying the asexual forms of *Pl falciparum*, and could therefore be employed as malarial suppressants with curative potentialities In the case of *Pl vivax* infections, however, they have proved ineffective as suppressants

In view of the variable therapeutic results obtained both in human and in experimental malaria in laboratory animals, it is clear that the plasmocidal value of the sulpha drugs is definitely inferior to that of either quinine or mepacrine

CERTUNA (CILIONAL)

This drug is stated to be dialkylamino-oxyquinolaminobutane, and like pamaquin is gametocidal, but is much less toxic than pamaquin

The dosage schemes advocated so far are as follows

(*a*) 0·07 G thrice daily for seven days (Sioli)

(*b*) 0·12 G daily for six days (Missiroli and Mosna)

SPECIFIC TREATMENT OF ACUTE BENIGN MALARIA IN THE EUROPEAN

The treatment of acute benign malaria aims at the rapid control of the febrile paroxysms, which, though seldom dangerous, nevertheless cause the patient acute distress and may subsequently give rise to a state of post malarial debility

It is generally agreed that the control of the febrile phase is relatively easy even though no standard procedure to this end has ever been laid down The prevention of relapses, however, is much more difficult, and in view of the uncertainty in this regard, most clinicians are content to eliminate the acute attack and simply deal with the relapses when they occur

Since the parasites are most vulnerable at the time of their release from the red cells, the plasmocidal efficacy of the drug employed will be greatly enhanced by synchronising its maximum concentration in the blood stream with sporulation In clinical practice, however, this is difficult to accomplish, hence treatment aims at maintaining an adequate concentration of the drug in the blood stream through out the 24 hours As the paroxysms will often be found to occur in the course of the forenoon it will generally be unnecessary to administer the drug during the hours of sleep

As already stated, absolute uniformity in the treatment of acute malaria has not yet been reached, but the following procedures have been found to constitute a suitable basis for the treatment of acute benign malaria

With the diagnosis established and the patient in the grip of an acute febrile paroxysm, one of the following procedures may be adopted —

1 Quinine sulphate is given in solution in a dosage of 10 grains thrice daily and continued until the patient has remained afebrile for 48 hours, after which the dosage is reduced to 10 grains twice daily for a further five days An alkaline solution consisting of 30 grains of sodium bicarbonate and 30 grains of sodium citrate is given twice daily throughout the period of quinine therapy, but to obviate precipitation of the alkaloid it must never be given together with the quinine solution

2 Where vomiting interferes with oral medication 10 grains of quinine are administered intramuscularly and repeated in 12 hours time after which it should be possible to complete the quinine course orally.

3 A very satisfactory procedure consists in controlling the febrile phase by means of quinine as described above and following through with mepacrine 0 1 G thrice daily for five days

4 Mepacrine may be employed throughout the entire course of treatment as follows

(a) Orally 0 3 G thrice daily for one or two days, 0·2 G thrice daily the next day, and 0·1 G thrice daily for a further five days, or

(b) an initial dose of 0·375 G of mepacrine methane sulphonate intramuscularly may be considered necessary to expedite control of the attack, after which the mepacrine course may be completed orally as indicated above

5 Recent observations on the therapeutics of *Pl vivax* infections indicate that the lowest relapse rates are obtained when the infection is treated with a combination of quinine and pamaquin in either of the following ways

(a) Ten grains of quinine and 0 01 G of pamaquin thrice daily for 10 days (This course calls for constant medical supervision and the immediate withdrawal of pamaquin at the first sign of toxicity)

(b) An intermittent course spread over a period of 31 days as follows 10 grains of quinine and 0 01 G pamaquin thrice daily for seven days followed by a seven-day rest period The dosage scheme is resumed for a further period of five days and after a further interval of seven days, the five day course is repeated for the last time

Toxic manifestations are seldom encountered during the "intermittent" course and recurrences are remarkably few

6 Paludrine will effect a clinical cure in all forms of acute benign malaria As a suitable overall course 0.3 G daily for 21 days is recommended To prevent relapses a maintenance dosage of 0 1 G twice weekly for at least six months will be necessary

Finally, whichever procedure has been followed, after a two-day rest in which no drugs are taken, the treatment course is rounded off with pamaquin 0 01 G thrice daily for three days

THE SPECIFIC TREATMENT OF ACUTE MALIGNANT MALARIA

In the treatment of acute malignant malaria, speedy control of the attack is of paramount importance if the dangerous pernicious forms are to be averted Indeed it may be said that the occurrence of such forms usually means that treatment has been either delayed or inadequate Consequently the main therapeutic objective in acute malignant malaria is the rapid introduction of an appropriate loading dose of the plasmocidal drug followed by the maintenance of an adequate concentration in the blood stream, throughout the treatment course To this end the procedures laid down for the treatment of acute benign malaria apply, although in malignant malaria it will frequently be found necessary to employ intramuscular medication in the initial phases of the attack

Before deciding upon a definite line of therapy in any given case it is necessary to ascertain—

1 Is there a history of blackwater fever?
2 Is there a history of hypersensitivity to quinine?
3 In the appropriate circumstances is there a co-existing pregnancy?

Where a positive reply is obtained to any of these questions it is advisable to use mepacrine rather than quinine It must be emphasised, however, that there is no hard and fast rule of procedure in the treatment of acute malignant malaria, but the usual lines of approach may be summarised as follows

1. Quinine sulphate is given orally in solution starting with 15 grains and following up with 10 grains thrice daily until the temperature has been normal or subnormal for seven days
2 In the presence of persistent vomiting, a heavy concentration of plasmodia in the peripheral blood or the threat of pernicious symptoms, 10 grains of quinine are administered intramuscularly, and the dose repeated in 12 hours or earlier if need be If after the second injection the attack appears to be well under control, the treatment course can then be completed orally by means of quinine (10 grains thrice daily as already described) or by means of the mepacrine dosage scheme already described

3 Mepacrine may be employed throughout the attack, and in the special circumstances enumerated above it constitutes the drug of choice Where rapidity of action is clearly necessary, mepacrine is given intramuscularly and the dose repeated in six hours Thereafter it will usually be possible to complete the treatment course orally Where oral treatment is possible from the outset the dosage scheme is the same as that advocated in the treatment of acute benign malaria

4 Paludrine it is claimed, will effect a radical cure in doses of 0 1 G thrice daily for 10 days or 0 1 G twice daily for 14 days

5 After an interval of two days a course of pamaquin is given (0 01 G thrice daily for three days), where quinine or mepacrine have been employed

TREATMENT OF THE MAIN PERNICIOUS FORMS

1 ALGID MALARIA

The dangerous state of vasomotor collapse which characterises this variety of malaria calls for prompt and expeditious relief *pari passu* with the treatment of the malarial infection Hence the treatment of algid malaria consists in

1 The administration of 5% glucose saline by the intravenous drip technique This procedure is combined with

(*a*) the maintenance of adequate warmth to the body, and

(*b*) 10 mg of desoxycortone daily by injection until the blood pressure has been restored to normal levels

2 Quinine (10 grains) or mepacrine methane-sulphonate (0 375 G) is injected intramuscularly and the dose repeated after six hours If after 12 hours no clinical improvement is evident it will then be wiser to give 10 grains of quinine intravenously through the tube of the drip apparatus, and in view of the prevailing vasomotor depression it is important to give 10 minims of 1 in 1,000 adrenalin solution at the same time and by the same route

Once the patient has recovered from the algid state the treatment course may then be completed by means of mepacrine orally

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2 CEREBRAL MALARIA

It may be said that the best treatment of cerebral malaria is centred in the prompt recognition and efficient control of every case of acute malaria But in children especially, or in the case of newcomers to a malarious district cerebral symptoms may set in with alarming rapidity, and in such circumstances a clear concept of the therapeutic procedure is essential Treatment aims at the speedy arrest of sporulation within the cerebral capillaries, and only by rapidly flooding the entire circulation with a powerful plasmocidal drug can this be achieved Any delay in the absorption of the drug will gravely jeopardise the patient's chances of recovery, hence intravenous therapy constitutes the method of choice in this dangerous form of malaria Various procedures have been advocated, but the following regime has been found satisfactory over a period of several years

1 Ten grains of quinine hydrochloride are given intravenously and repeated in six hours if no apparent clinical improvement has taken place

2 Lumbar puncture is performed soon after the intravenous instillation of quinine, and the cerebro-spinal fluid is drained away until a normal rate of flow from the lumbar puncture needle is observed

   Lumbar puncture may not be deemed necessary in every case of cerebral malaria, but it should always be regarded as an essential therapeutic measure in all cases showing clinical evidence of the onset of coma This procedure probably has the effect of improving the concentration of quinine in the cerebral circulation

3 Glucose saline (5%) is administered intravenously by the slow drip technique Under "field conditions", however, this step may not be possible

4 When clinical improvement sets in, intravenous quinine therapy is replaced by quinine or mepacrine intramuscularly every 6 to 12 hours for two or more injections, and finally the treatment is completed orally

It may be noted that some clinicians prefer to employ mepacrine intramuscularly in the treatment of cerebral malaria, giving 0 375 G

of mepacrine methane sulphonate every six hours Good results are claimed for this method

The intravenous technique already described will usually be found effective in the treatment of cerebral malaria in the first 24 or 36 hours of the attack, but once this period has elapsed the therapeutic control becomes increasingly difficult and fraught with considerable hazard

From the nursing point of view, every case of cerebral malaria must be kept under constant supervision during the acute phase The face is kept turned to one side, and it is preferable to keep the head and shoulders slightly raised to give free play to the respiratory muscles

3 ABDOMINAL MALARIA

The treatment of abdominal malaria resolves itself into the prompt administration of a specific drug and the prevention of dehydration

1 The drug of choice in abdominal malaria is mepacrine in that it does not appear to aggravate the state of vasomotor hypotension which so frequently sets in as the attack develops Mepacrine is given intramuscularly, and the dose is repeated every six hours until sustained clinical improvement is apparent, when oral treatment can be instituted
2 Intravenous glucose-saline (5%) is given at the outset and maintained until all fluid loss has been made good and until the patient can take an adequate amount of fluid orally

SPECIFIC TREATMENT OF CHRONIC MALARIA

Once a diagnosis of chronic malaria has been established, a highly satisfactory response to one of the anti malarial drugs will usually be obtained It is probable that the efficacy of specific drug therapy is significantly enhanced by the state of premunity which it is reasonable to assume exists to a greater or less degree in all cases of chronic malaria At any rate it is seldom necessary to give a series of courses of drug therapy in chronic malaria

Mepacrine is an invaluable drug in all cases of this kind It is given orally at the rate of three 0 1 G tablets daily for a total of seven days

As a follow up measure N A B intravenously will always be found of great value It may be given in three doses of 0 3 G at weekly intervals

THE SPECIFIC TREATMENT OF MALARIA IN THE AFRICAN

When an adult African develops clinical evidence of malaria, an elaborate course of specific therapy is both unnecessary and undesirable

The native of the kraals or the native living under conditions which expose him to reinfection is largely dependent on a continuing state of premunity to protect him against acute attacks of malarial fever, so that any treatment which aims at complete elimination of his infection is thoroughly unsound from the immunological viewpoint When, therefore, an African native develops an acute malarial pyrexia, a logical and entirely satisfactory therapeutic procedure consists in administering·

(*a*) 10 grains of quinine twice daily, or

(*b*) one 0 1 G tablet of mepacrine twice daily until the temperature has been normal for a day

When this line of treatment is adopted, the course of specific therapy will rarely last for more than one to two days

In the case of infants and young children, however, acute malaria may be a serious disease, so that a more vigorous and protracted course of treatment becomes necessary Using appropriately modified doses of quinine or mepacrine, the procedure to be followed is essentially the same as that described for the European

CHAPTER EIGHT

PREVENTION

As the wider issues inherent in the problem of malaria prevention fall outside the scope of what is essentially a clinical monograph, the discussion will be confined to the question of chemoprophylaxis from the view point of the individual

Until quite recently the quest for a true causal prophylactic in malaria had proved unavailing, but preliminary trials with Paludrine hold out considerable promise of the effective chemical control of the disease in the pre-clinical phase

It may be said that wherever Europeans live in an area of endemic malaria it is clearly necessary to supplement all other prophylactic procedures by means of chemoprophylaxis Where the disease persists in an active form throughout the year, then continuous chemoprophylaxis becomes necessary, but in most parts of Africa at least malaria has a distinct seasonal incidence, so that a more restricted scheme of suppressive treatment becomes possible In such circumstances it will suffice if the treatment is begun immediately ahead of the "season" and continued for six weeks after the danger period has passed Furthermore it is important to adhere conscientiously to the dosage scheme adopted particularly in the case of quinine prophylaxis, as it is generally held that the erratic quinine taker appears to show an enhanced susceptibility to blackwater fever

The following drugs are available in the prevention of malaria (1) Quinine, (2) Mepacrine, and (3) Paludrine

QUININE PROPHYLAXIS

Two methods of quinine prophylaxis have been evolved (*a*) the daily small dose of quinine which until quite recently has been the method of choice throughout the tropical belt of the British Colonial Empire, and (*b*) the intermittent method originally advocated by Koch

In the case of adults the daily method of quinine prophylaxis consists in taking 5 grains (0 325 G) of quinine at sunset or preferably 5 grains night and morning Children from four to 12 years

receive 3 grains (0 2 G) daily Children under four years receive ¾ grain (0 05 G) for each year of life For children over 12 years 6 grains (0 4 G) is recommended

The intermittent method of quinine prophylaxis originally advocated by Koch consisted in taking a large dose of quinine every tenth day Koch's procedure has since been modified by shortening the interval between doses and now consists in taking 15 grains (1G) daily on two consecutive days in each week Nocht advocates five doses of 3 grains (0 2 G) or four doses of 0 25 G daily on each of the two days in question, while Ziemann favours 15 grains (1 G) every fourth day

Neither method of quinine prophylaxis will prevent infection, nor will it ensure complete freedom from clinical attacks in bad malarious regions, but severe and dangerous attacks will usually be averted, whichever method of prophylaxis is adopted Finally, the clinical evidence available suggests that side effects such as myocardial weakness, defects of hearing or of vision are not encountered in the course of quinine prophylaxis

MEPACRINE PROPHYLAXIS

Experience during the war years has amply demonstrated the outstanding value of mepacrine as a malarial suppressant, together with its great superiority to quinine in this regard

The dosage recommended is 0 1 G daily This dosage scheme is initiated a week or two before the onset of the malaria season, to allow time for an effective build up in plasma mepacrine It is maintained throughout the season and for six weeks after the risk of infection has passed By this means infections with the *Pl falciparum* will be eliminated and the risk of clinical attacks following the cessation of suppressive treatment virtually removed In the case of infections with *Pl vivax*, however, overt clinical attacks will be held in check throughout the period of suppressive treatment, but an acute attack invariably develops within a few weeks of its cessation

No toxic symptoms of any significance are associated with mepacrine prophylaxis on the dosage scheme outlined above, apart from occasional transient gastric discomfort during the first two or three days of the treatment Yellow tinting of the skin, however, occurs in most cases but varies considerably in depth The pigmentation is

usually most noticeable in relation to the dorsum of the hands and feet and on the face

PALUDRINE PROPHYLAXIS

While it is not yet possible to make a final assessment of the prophylactic value of paludrine in relation to all varieties of African malaria, it has been shown above that by reason of its lethal action on the pre erythrocytic forms of the plasmodium it constitutes a complete causal prophylactic in *Pl falciparum* infections and a partial causal prophylactic in the benign forms

The dosage scheme at present recommended for prophylactic purposes is 0 1 G every Wednesday and Sunday throughout the malaria season

ADDENDUM

PALUDRINE

Since the account of the paludrine treatment of malaria was written the drug has become available for the treatment of the disease in Africa, and the experience gained to date has revealed the fact that the drug fails to bring about the rapid control of the febrile paroxysms as claimed in the original publications Thus pyrexias conditioned by the Rhodesian strains of *Pl falciparum* continue unabated for three or four days after the introduction of paludrine therapy, while severe attacks of malignant malaria have occurred in spite of systematic paludrine prophylaxis

It is clear from these findings that some modification in the description of the therapeutics of paludrine in relation to the African forms of malaria will be necessary

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